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THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and for the reporting of research and observation in the domain of internal medicine.

Manuscripts for publication, books for review and correspondence relating to the editorial management should be sent to the Chief Editor, Dr. Paul S. Rhoads, 535 North Dearborn Street, Chicago 10. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago 10.

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Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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A. M. A.
ARCHIVES of INTERNAL MEDICINE

VOLUME 86 OCTOBER 1950 NUMBER 4

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# CLINICALLY THE MYOCARDIUM

HENRY A. CHRISTIAN, M.D.

Hersey Professor Emeritus of Theory and Practice of Physic, Harvard University, and Physician-in-Chief Emeritus, Peter Bent Brigham Hospital, Boston

BROOKLINE, MASS.

AS A CLINICIAN of the past seeing present day medicine through the clinical and investigational eyes of today as delineated in medical journals, I have gained the idea that, to those particularly interested in the circulatory system of man, the myocardium has been losing clinically in its interest, with the exception of its consideration as a terrain for changes in electrical potential which are traced in, and interpreted from, electrocardiograms of many leads. This attitude does not seem to me to be justified, when we give consideration to the complexity of structure and function of the myocardium and their potentiality to be influenced by conditions of disease in man.

Some of my younger colleagues decry my frequent usage of the term "myocardial insufficiency" and my belief in its clinical importance. To me myocardial insufficiency is a condition in which "there is evidence during life of failure of the heart muscle to function with normal efficiency." That is my definition of it. One of these colleagues commented, "I think we do better confining our discussion to those things we can measure, if only with poor accuracy. Apparently you are not tortured, as I am, with the thought that many conditions now regarded as 'myocardial insufficiency' are going to turn out to be due to trouble in the kidney or in the endocrine glands and not to the heart at all." Granting the reasonableness of these torturing thoughts of his, still I believe that many causes not within the heart work, even though indirectly, just as do many causes within the heart to produce myocardial insufficiency as I have defined it, and that the myocardium does have a role of primal importance in efficient function of man's circulation.

## CLINICAL AND PATHOLOGIC EVIDENCE

I believe that in very many patients with symptoms and signs of heart disease the chief cause lies in a defective or deficient functioning of the myocardium rather than of the heart valves and the peripheral vascular

Read by title at the meeting of the Association of American Physicians, Atlantic City, N. J., May 3, 1950.

trees. What clinical and pathologic evidence have we of this importance of the myocardium? We know that acute infectious diseases with great frequency cause disturbances in its function and/or in its structure. During the febrile stage of many of the acute infectious diseases the electrocardiogram shows departures from normal indicative of some lesion in the heart muscle. This is notably true of acute rheumatic fever. Often these changes are temporary, since repeated electrocardiograms show that the abnormalities disappear during convalescence and the tracing returns to normality. However, this does not always happen, and in an occasional patient the changes persist or even increase. In other words, if these electrocardiographically recorded changes represent lesions in the myocardium, as they seem to do, many of them are reversible and disappear, but some are irreversible and persist or increase. That histologically demonstrable lesions are often present in the myocardium during an acute infectious disease is shown by the frequent finding in the hearts of patients, who died in the course of an infectious disease, of focal or diffuse lesions, such as degenerative changes in muscle cells or their nuclei, edema of the myocardium, cellular infiltration in, and proliferation of, the intercellular connective tissue and various lesions of the arterioles, capillaries and venules of the myocardium. Many of these probably would have healed completely, or possibly incompletely, had the patient survived the acute infectious disease, while other acute lesions of the nature just cited presumably would not have healed, particularly when they were extensive. Some patients with acute infectious disease during the acute phase or later on show symptoms and signs of cardiac decompensation from which they gradually recover, or which may be an important or the most important factor in their death. In these autopsy almost always shows extensive focal or diffuse lesions of the myocardium diagnosed by the pathologist as acute, subacute or chronic myocarditis, depending on the time between their inception and the death of the patient.

The type of pathologic lesion just described also occurs in patients with extensive changes of unknown causation or in those at least in whom there has not been any preceding diagnosable acute infectious disease and in whom attempts to isolate a causative bacterium or virus have failed. These cases are called isolated, or Fiedler's, myocarditis and constitute a definite clinical entity. Possibly they are of viral origin, because there occurs at times in animals a histologically similar cardiac lesion of viral origin which can be propagated by inoculation from animal to animal. We know, too, of a trypanosomal disease in South America with extensive myocardial lesions, American trypanosomiasis or Chagas' disease. In other words, we know of the frequent occurrence of both reversible and irreversible acute, subacute and chronic myocarditis of both known and unknown causes.

### CHRONIC NONVALVULAR HEART DISEASE

It is known that acute rheumatic fever may inaugurate cardiac lesions which many years later will progress into chronic heart disease that eventually is fatal. One wonders if it is not possible that those frequent cases of chronic nonvalvular disease not caused by hypertension may not have had their inception in acute lesions of the myocardium which appeared during the course of some acute infectious disease. Since almost every patient has had at some time one or several bouts with an acute infectious disease, this idea cannot be proved or disproved on a statistical basis, although there is increasing evidence that infectious diseases often do cause persisting vascular lesions, and, thus, possibly myocardial ones as well.

There is also clinical and pathologic evidence that in patients with both chronic valvular and chronic nonvalvular heart disease periods of decompensation often are inaugurated by an attack of an acute infectious disease, including recurrent acute rheumatic fever. After some of these attacks, which were fatal, postmortem study has shown acute lesions in the myocardium recognizably of rheumatic origin, as well as lesions of indeterminable causation. Recent pathologic and immunologic studies have accentuated the importance of acute rheumatic fever in causing the death of such patients who have had long-standing heart disease, and it is probable that acute nonrheumatic infectious disease may do the same thing.

Chronic nonvalvular heart disease occurs with great frequency, equaling the incidence of chronic valvular, i. e., rheumatic, heart disease at about 40 years of age and thereafter increasing in ratio, until after 60 years of age it affects well over 90 per cent of patients showing clinical or pathologic evidence of heart disease. Hypertension and coronary artery lesions are causative of nonvalvular heart disease, or at least present, in about two thirds, possibly three fourths, of these patients, but in the remainder neither of these conditions is causative. Syphilis only rarely is a causative factor. Seemingly, cardiac hypertrophy for some reason has been started; when it passes a certain degree, cardiac failure with progressing dilatation of auricles and ventricles results, and the patient displays symptoms and signs of chronic heart disease. Histologic examination of these hearts sometimes shows focal or diffuse connective tissue increase, but often none is observed, and the only demonstrable change from normal is increase in the size of the muscle cells. Apparently some acute change or strain has caused dilatation, followed by hypertrophy and a continuing chain of dilatations, followed by increasing hypertrophy in an irreversible succession that eventuates in cardiac decompensation as described in a subsequent paragraph. Clinically this form of heart disease is important.

In all the changes in the myocardium that so far have been described, usually there is an accompanying arrhythmia, which may put an additional burden on the circulation; however, so far as we know, these arrhythmias are not a cause of myocardial lesions but rather an expression of an irritability resulting from the myocardial lesion or a reflex from various changes in the heart, including dilatation of the cardiac cavity. The ease with which arrhythmias can be produced is evidenced by their almost constant presence from the irritation caused by a catheter introduced into the auricle or ventricle in one of the modern technics of cardiology, as shown on continuous electrocardiograms recorded during catheterization of the heart. Fortunately, only rarely is an arrhythmia caused in this way fatal, and so we know little of the injury to endocardium and myocardium that has resulted in man from a catheter in the heart, but we do know that in dogs thrombi and other lesions of the endocardium and myocardium are a frequent sequence or consequence of such catheterization.

## VULNERABILITY OF THE MYOCARDIUM

The vulnerability of the myocardium, as already indicated, is appreciated if we review briefly its function and structure. It then becomes evident that minor disturbances or lesions of the myocardium can, and often do, result in those serious disturbances in cardiac function which we know as heart disease, more particularly as myocardial insufficiency in nonvalvular heart disease.

In the heart muscle arise various reflexes which follow nerve paths to the brain and back to various body tissues. Some of these are of known clinical importance, such as the reflex from heart to brain and back to the stomach and the one from heart to brain and back to the colon which make known an excess in digitalis therapy by loss of appetite, nausea, vomiting and/or diarrhea. Recently, knowledge has been obtained of another reflex pathway from heart to brain, originating in a particular part of the myocardium, namely, the left ventricle, possibly in the endocardium and subendocardial muscle, through which drugs, such as alkaloids of veratrum viride, produce their effect on pulse rate and blood pressure. Possibly other localized cardiac reflex centers will be demonstrated with reflex pathways from heart to brain and back to various body tissues and become of clinical and therapeutic importance.

Heart muscle in many respects resembles skeletal muscle. Like skeletal muscle, it is composed of striated, nucleated fibers or cells with a rich blood supply and a slight connective tissue supporting framework. Unlike skeletal muscle, it is continuously contracting (systole) with interspersed periods of rest (diastole). This failure to rest for any continued period necessitates a constant activity of metabolic changes, again unlike skeletal muscle in which fatigue sensations and accumulated

catabolic products will indicate the need for, and will lead to, periods of rest for the length of time required to remove the sensation of fatigue and to restore metabolic equilibrium.

After the myocardium reaches its full development, there is almost no additional formation of contractile cells and blood capillaries about them, if and when the myocardium increases in weight. For such an actively and continuously contracting and relaxing tissue as is the myocardium, there is need in each muscle cell and nucleus for a continuous, large supply of the materials required for their anabolism and the removal of the materials resulting from their catabolism.

Optimal and maximal efficiency in the function of the myocardium, chiefly its continuing rhythmic contraction and relaxation, can be decreased in a number of ways. Toxic substances, if they reach the heart muscle, and they often do, can and do cause injury to heart muscle cells and their nuclei, with resultant decrease in their potential activities. Often toxins produce visually demonstrable evidences of degenerative changes in muscle cells, and less frequently in nuclei, which up to a certain point are reversible with return to complete normality of structure and function, but beyond this point they become irreversible and may or may not be progressive, so that normality does not return. These injured myocardial cells function with a decreased efficiency.

The spatial relations of capillary to muscle cell and nucleus are important. If muscle cells increase in size, as they do when the heart hypertrophies, changes in cell nutrition take place; the cell being larger needs more nutrients, and to reach the nucleus in the enlarged cell the nutrient substances must travel a longer distance from the peripherally situated capillary. In the opposite direction products of catabolism of cell and nucleus must be removed over a greater distance and probably in increased amount. These distances are increased still more for some parts of the cell because, since the capillaries do not increase in number with cardiac hypertrophy, they become spaced more widely about each muscle cell. Furthermore, because of this failure to increase in actual number, the capillaries are fewer in ratio to the now enlarged muscle mass, with the result that there is less blood available for the metabolic activities of cell masses, which have increased through the increase in size of the individual cell, while these cells actually need more of the circulating nutrients and should have a greater removal of waste products of cell catabolism. Decreased myocardial function eventually results from these changes and can be expected when heart weight reaches 500 to 600 Gm., sometimes much sooner. Somewhat the same relationships of lymph channels to muscle cells hold as for those of capillaries to muscle cells just enumerated and are further contributory to cardiac insufficiency.

If, as the result of the action of toxic substances, edema of the myocardium ensues, the edema fluid around the muscle cells or fibers increases the spatial relations of capillary and lymph channel to muscle cell and nucleus. As a result there is a less active flow to and from cells and nuclei of material needed in their anabolism and catabolism. Toxic substances, besides causing edema, often cause inflammatory lesions, with cellular infiltration into the connective tissue framework or with connective tissue proliferation, both of which, just as edema does, hinder the passage of substances of importance in metabolism to and from blood vessels to muscle tissue.

Then if toxic reactions cause changes in capillary walls, and this they often do, these again act to decrease intercellular and intracellular exchange of anabolic and catabolic materials. Furthermore, any thickening or degeneration of the walls of the capillaries, arterioles and venules in the myocardium caused by injurious agents will decrease blood flow through them, impede supply of needed nutrients and slow drainage of waste products. Edema in and about the cells of the myocardium and infiltration of cells into, and proliferation of, the connective tissue framework also restrict effective contraction and relaxation of the myocardium.

The cardiac muscle mass forms the wall of the heart cavities and by its contraction produces blood flow in the pulmonary and peripheral vascular trees to carry nutrient materials. The size of these cardiac cavities varies with each systole and diastole, and there are slower changes in size influenced in many ways, usually referred to as changes in tonus. Distention or dilatation of heart cavities leads to more vigorous contractions and slowly stimulates thickening of the muscle wall, or hypertrophy, a process which at first is reversible but which in time becomes irreversible, with a decreasing outflow and an increasing diastolic residual of blood. This mechanism has fundamental importance in the causation of the continuing hypertrophy of the heart in chronic nonvalvular cardiac disease; the hypertrophy, as it develops, is accompanied with enlargement of the individual muscle cells without increase in the number of peripherally situated capillaries. This in return, as already explained, brings about a lessened exchange of increased products of muscle cell metabolism between cells and capillaries and a consequent decrease in functional efficiency of the myocardium. The initiation of the dilatation, which in a recurring cycle of dilatation and hypertrophy leads to myocardial insufficiency, as far as we know, goes back to an injury of the myocardium during the course of an acute infectious disease or to some acute strain on the heart.

These are some of the many important activities of the myocardium and the factors influencing them which must be taken into account in any clinical consideration of the myocardium.

SUMMARY

The clinical importance of the myocardium is emphasized. The term myocardial insufficiency is defined and its use defended. Clinical and pathologic evidence of the importance of the myocardium is emphasized. The frequency of myocardial lesions during the course of, or subsequent to, acute infectious diseases is pointed out, whether indicated in electrocardiograms or demonstrated in postmortem studies. The great frequency of chronic nonvalvular heart disease is indicated. The vulnerability of the myocardium is stressed on the basis of its function and structure in relation to injurious agents and to its hypertrophy, in which the size of muscle cells but not their number increases, with the number of capillaries about them remaining unchanged. This results in a larger cell mass receiving a lessened supply of nutrients for anabolism and a less efficient removal of the products of catabolism.

# AUREOMYCIN IN PREVENTION OF BACTEREMIA FOLLOWING TOOTH EXTRACTION

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SINCE the advent of antibiotics, the prognosis of subacute endocarditis has been improved greatly; nevertheless the disease is still fatal in about 50 per cent of patients. It is by no means a rare sickness, particularly in areas where rheumatic heart disease is common. Patients with subacute bacterial endocarditis will, in almost every case, have had either a preexisting lesion of one of the cardiac valves or a congenital cardiac deformity. The valvular lesion may have been caused by rheumatic fever, syphilis or arteriosclerotic changes and is often unknown to the patient. Lesions due to arteriosclerosis are of special importance because they are the nidus on which bacterial infection develops in older persons. The majority of patients, however, are between 20 and 40 years of age, the sexes being almost equally afflicted.

The commonest organism causing subacute bacterial endocarditis is Streptococcus viridans. When this organism causes a transitory bacteremia in a healthy person, it is readily destroyed by the defenses of the body or it is excreted before it can do any harm. If, however, the endocardium has been injured by one of these previously mentioned conditions, the Str. viridans may implant itself on the damaged leaflets and cause subacute bacterial endocarditis, even though the bacteremia lasts only a few minutes.

Str. viridans is present in the mouth of healthy persons but grows particularly well when gum infection or dental decay develops.

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These infected areas constitute foci of infection from which showers of organisms may be disseminated repeatedly by the daily trauma of chewing or by operation.[1] For this reason, it is of the utmost importance to eliminate the source of infection in persons with heart disease. However, the dental manipulation necessary to remove a focus of infection in persons with damaged heart valves or congenital heart disease may cause a bacteremia and precipitate subacute bacterial endocarditis.[2] Particular caution, therefore, is necessary in these patients prior to tooth extraction or any other dental manipulation, especially when infection is present, in an effort to reduce the high incidence of transient bacteremia following such operations. Therapeutic agents, such as sulfadiazine[3] and sulfapyridine,[4] have been employed prior to and following dental operations. However, use of these drugs has not always been successful[3b]; in addition, they are potentially toxic agents which may cause damage to the kidneys, blood vessels, skin and blood. Recently, gantrisin® (3, 4-dimethyl-5-sulfanilamido-isoxazole), a new sulfonamide,[1b] was administered because it is supposedly less toxic.

Penicillin in oil has also been used and has helped to reduce the occurrence of bacteremia substantially.[1b, c] Penicillin, however, has the disadvantage of not infrequently causing allergic reactions and of being reliable only when given by injection. This procedure is disliked by many dentists and patients and is, therefore, often omitted, at times with fatal consequences. For these reasons, we searched for an antibiotic with a broad therapeutic bacterial spectrum which can be given successfully by mouth, which is relatively nontoxic and which does not create

1. (*a*) Okell, C. C., and Elliot, S. D.: Bacteriæmia and Oral Sepsis, with Special Reference to Ætiology of Subacute Endocarditis, Lancet **2**:869 (Oct. 19) 1935. (*b*) Rhoads, P. S., and Schram, W. R.: Bacteremia Following Tooth Extraction: Prevention with Penicillin and a New Sulfonamide, Gantrosan, read before the Ninety-Eighth Annual Meeting of the American Medical Association, Atlantic City, N. J., June 8, 1949. (*c*) Hirsch, H. L.; Vivino, J. J.; Merrill, A., and Dowling, H. F.: Effect of Prophylactically Administered Penicillin on Incidence of Bacteremia Following Extraction of Teeth: Results in Patients with Healed Rheumatic and Bacterial Endocarditis, Arch. Int. Med. **81**:868 (June) 1948.

2. (*a*) Feldman, L., and Trace, J. M.: Subacute Bacterial Endocarditis Following Removal of Teeth or Tonsils, Ann. Int. Med. **11**:2124 (June) 1938. (*b*) Geiger, A. J.: Relation of Fatal Subacute Bacterial Endocarditis to Tooth Extraction, J. Am. Dent. A. **29**:1023 (June) 1942. (*c*) Footnote 1 *b* and *c*.

3. (*a*) Geiger.[2b] (*b*) Clement, D. H., and Montgomery, W. R.: Subacute Bacterial Endocarditis: Report of a Case with Apparent Failure of Sulfonamide Prophylaxis Complicated by Massive Hemoperitoneum, Ann. Int. Med. **22**:274 (Feb.) 1945.

4. Clagett, A. H., Jr., and Smith, E. H., Jr.: Subacute Bacterial Endocarditis and Dental Extraction, J. Am. Dent. A. **28**:1841 (Nov.) 1941.

resistant organisms. Aureomycin [5] met these requirements and was, therefore, used exclusively in our series.

## METHODS OF STUDY

As the successful action of aureomycin in preventing bacteremia was yet unknown, only patients without heart disease were included in this series. All patients were hospitalized for three days, during which they were carefully examined to rule out any cardiac disease. Patients with heart murmurs or patients who gave a history of rheumatic fever, chorea or any previously diagnosed congenital heart disease were excluded. The patients were divided into four classes from the dental point of view:

Class I.—Unerupted or impacted teeth with no roentgenologic or clinical evidence of infection

Class II.—Impacted or partially erupted teeth with moderate pericoronal infection

Class III.—Multiple teeth with moderate amount of periapical and periodontal infection

Class IV.—Extensive periapical and periodontal infection of multiple teeth

Every other patient received aureomycin; the alternate patients served as controls. The patients were unselected, except for the absence of heart disease. On distributing the 25 patients in the treated and the untreated groups according to their dental classification, one finds in the untreated group 1 patient in class I, 8 patients in class II, 10 patients in class III and 6 patients in class IV. In the treated group 1 patient belonged to class I, 7 patients to class II, 7 patients to class III and 10 patients to class IV. On comparing these figures, one finds classes I and II about equally represented, while lesions of class III occurred more commonly in the untreated group and lesions of class IV more commonly in the treated group. Aureomycin was given on the day before the extraction, on the same day and on the day after. Two grams of aureomycin, divided in four doses, was given every day. The average preoperative amount was 3 Gm. of aureomycin. The usual interval between the last dose and extraction was three hours. The control group received no medication at any time. All operations were performed with the patient under general anesthesia induced with thiopental (pentothal®) sodium and oxygen, at times supplemented with nitrous oxide. All patients remained in the hospital for 24 hours following the procedure.

Bacteriologic studies were carried out on each patient. A blood culture was taken on every patient at his bedside prior to operation and medication. About 15 cc. of venous blood was withdrawn, with sterile technic. Eight cubic centimeters was added to a flask containing 75 cc. of tryptose phosphate broth with paraaminobenzoic acid. Five cubic centimeters of the blood was added to 0.5 cc. of a 3 per cent solution of sodium citrate. This blood was taken immediately to the laboratory.

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5. Finland, M.; Collins, H. S.; Gocke, M., and Wells, E. B.: Present Status of Aureomycin Therapy, Ann. Int. Med. **31**:39 (July) 1949. Spink, W. W., and Yow, E. M.: Aureomycin: Present Status in the Treatment of Human Infections, J. A. M. A. **141**:964 (Dec. 3) 1949. Aureomycin was supplied by J. M. Ruegsegger, M. D., Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

In the laboratory the broth was placed in the incubator. A pour plate was made by adding 2 cc. of citrated blood to a tube containing 20 to 25 cc. of a 1 per cent dextrose blood agar base with paraaminobenzoic acid. Finally, 2 cc. of the citrated blood was added to 15 cc. of thioglycollate broth for anaerobic growth.

This same procedure was repeated on every patient immediately following the extraction and half an hour later. Each culture was incubated at 37.5 C. (98.6 F.) for ten days. It was checked each day; if growth appeared, a subculture was taken for identification. The cultures were discarded after ten days if they remained sterile.

## RESULTS

Of 25 patients who had not received any antibiotic, 14 had blood cultures positive for Str. viridans immediately following tooth extraction. Each showed good growth of Str. viridans in the broth, and, in addition,

*Incidence of Blood Cultures Drawn Immediately After Tooth Extraction Which Were Positive for Streptococcus Viridans in Control and Treated Patients According to Dental Classification*

| | Untreated Patients | | | Treated Patients | | |
|---|---|---|---|---|---|---|
| Dental Class | No. of Patients | Str. Viridans in Blood Cultures | % of Total Patients | No. of Patients | Str. Viridans in Blood Cultures | % of Total Patients |
| I..... | 1 | 1 | 4 | 1 | 0 | 0 |
| II. ..... | 8 | 5 | 20 | 7 | 1 | 4 |
| III..... | 10 | 6 | 24 | 7 | 0 | 0 |
| IV..... | 6 | 2 | 8 | 10 | 0 | 0 |
| Total..... | 25 | 14 | 56 | 25 | 1 | 4 |

pour plates of 11 of these patients grew one to 12 colonies of the organism. In two of these patients Str. viridans was also found in the flask with thioglycollate broth. The blood cultures of the remaining 11 patients of this group were negative for Str. viridans, but two of them showed a good growth of nonhemolytic streptococcus in the broth. Another showed one colony of pneumococci on the pour plate. In one patient a good growth of staphylococcus in addition to Str. viridans appeared in the broth.

Among 25 patients who had received aureomycin, only one blood culture positive for Str. viridans was found. The blood cultures of the remaining 24 patients were negative for this organism. On four occasions, however, a good growth of Staphylococcus pyogenes var. albus was noted in the broth, and two of these patients also showed a growth of staphylococcus on the pour plate. In all the cases in which Staph. pyogenes var. albus was found, the reaction to the coagulase test was negative, indicating that this organism was probably a contaminant. None of the cultures taken either before extraction or half an hour after extraction showed any growth (table).

## COMMENT

The results of these studies show that administration of aureomycin is of definite value in decreasing the transient bacteremia with Str. viridans which follows tooth extraction. This was true even though the aureomycin-treated group included the greater number of patients with extensive infection who consequently received more extensive surgical trauma. The difference between 56 per cent of blood cultures yielding Str. viridans in the untreated group and 4 per cent in the treated group is statistically significant. These results compare favorably with those obtained by Hirsch and his associates [1c] and Glaser and his co-workers [6] with penicillin and by Rhoads and Schram [1b] with penicillin or gantrisin.*

The importance of being able to decrease the incidence of bacteremia is obvious, if one considers the seriousness of subacute bacterial endocarditis and the frequency with which this disease occurs after tooth extraction and dental manipulation. For instance, during the years 1947 to 1949 inclusive, 19 patients with subacute bacterial endocarditis entered the New Haven Hospital. Of these 19 patients, two gave a history of dental extraction within a few weeks prior to the onset of their illness. One additional patient had had three teeth knocked out in an automobile accident, and still another had had dental prophylaxis vigorous enough to cause severe bleeding of the gums. None of these patients had received prophylactic antibiotics. These figures correspond well to those reported by Okell [1a] and Favour and his co-workers [7] in their studies. It is, therefore, self evident that prophylactic measures should be taken each time an operation is performed in any infected area on a patient with valvular or congenital heart disease.

Each physician, surgeon and dentist should assure himself that his patient does not have heart disease. When the diagnosis of valvular or congenital heart disease is made, the physician should notify the patient of his findings and should instruct him to ask for prophylactic antibiotic treatment before any operation and particularly before dental extraction. Every surgeon and dentist, on the other hand, should ask the patient whether he has heart disease and should get more exact information from the patient's family physician. If this is unobtainable, a history of previous rheumatic fever, chorea, dyspnea or cyanosis should be sought for. If such a history is obtained, the patient should have a careful cardiac examination before the operation is performed. In case of doubt, it is preferable to give prophylactic antibiotics.

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6. Glaser, R. J.; Dankner, A.; Mathes, S. B., and Harford, C. B.: Effect of Penicillin on the Transient Bacteremia Following Dental Extraction, abstracted, Am. J. Med. **3**:115, 1947.

7. Favour, C. B.; Janeway, C. A.; Gibson, J. G., and Levine, S. A.: Progress in the Treatment of Subacute Bacterial Endocarditis, New England J. Med. **234**:71 (Jan. 17) 1946.

It may be of interest that the only patient whose blood culture was positive for Str. viridans despite aureomycin administration had received the last preoperative dose of this drug by mistake 4½ hours before extraction, while the others had received it within three hours. In this one patient, the total preoperative dosage was 2.5 Gm., while in all other patients it was 3 Gm. This may be of importance in planning the schedule of medication. It seems logical, therefore, to give the last dose not more than three hours, and preferably two hours, prior to the operation. Positive blood cultures prior to medication and operation have been described by others, although they did not occur in any of our patients. For this reason, it is advisable to begin the medication at least 24 hours prior to the operation. This schedule of medication may help to decrease the number of bacteria which can enter the blood stream. The medication should be continued for at least 24 hours following tooth extraction because bacteremia may occasionally occur immediately following operation despite administration of antibiotics, as our studies and those of others [8] have shown. The continued use of aureomycin for one or two days following operation should help to eliminate these bacteria. One of us (A. L. C.) noted on follow-up examination that aureomycin-treated patients showed more rapid healing of the gums than those patients who did not receive any medication. This beneficial effect of aureomycin on the healing of gum infection has been reported by Jacobs and Jacobs.[9]

Only one of the patients in our series showed toxic manifestations of nausea and vomiting from the use of aureomycin. The symptoms were not severe enough to interrupt the medication. Although in our series general anesthesia could be used for the convenience of the patients, as they did not have heart disease, the production of local anesthesia with epinephrine and procaine may help further to decrease the incidence of bacteremia, as reported by others.[10] This type of anesthesia should be the one of choice for every patient with known valvular or congenital heart disease and will be employed in our forthcoming controlled study on the action of prophylactic use of aureomycin in patients with known heart disease.

8. Hirsch and others.[1c] Glaser and others.[5]

9. Jacobs, H. G., and Jacobs, M. H.: Aureomycin: Its Use in Infections of the Oral Cavity; A Preliminary Report, Oral Surg., Oral Med. & Oral Path. **2**:1015 (Aug.) 1949.

10. Villardo, S.: Immunity Phenomena in Procaine Hydrochloride Anaesthesia, Gior. di batteriol. e immunol. **20**:1201, 1938, cited by Hirsh.[1c] Burket, L. W.: Oral Medicine: Diagnosis, Treatment, Philadelphia, J. B. Lippincott Company, 1946, p. 233. Harrison, F. F.; Mayock, R. L., and White, W. L.: The Treatment of Bacterial Endocarditis, M. Clin. North America **30**:1235 (Nov.) 1946.

## SUMMARY AND CONCLUSIONS

Twenty-five controlled patients without heart disease received aureomycin orally in divided doses on the day before the dental extraction, on the same day and on the day after. Blood cultures were positive for Streptococcus viridans in 56 per cent of the untreated patients and 4 per cent of the patients receiving aureomycin. This difference is statistically significant. It is of clinical significance when it is realized that about 20 per cent of all cases of subacute bacterial endocarditis can be traced to recent dental manipulation. For this reason, every patient before an operation should be carefully questioned and examined for valvular or congenital heart disease. If such a condition is found, prophylactic antibiotic treatment should be given.

Aureomycin, in our opinion, is at present the drug of choice because it is successful in reducing the incidence of Str. viridans bacteremia; it can be given orally; it apparently does not produce drug-resistant organisms, and it has a relatively low toxicity.

Two grams of aureomycin daily in divided doses was used in our study. The last dose before the operation should be given not earlier than three hours before surgical intervention.

Drs. Francis G. Blake and Theodore S. Evans assisted in writing this report and Dr. Robert Nesbit in making the bacteriologic studies possible.

# EFFECTS OF INTRAVENOUS INJECTION OF TYPHOID VACCINE ON BLOOD LEUKOCYTES AND ADRENAL CORTEX

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THE OBSERVATIONS of Dougherty and White [1] on the effects of pituitary adrenocorticotropic hormone on lymphoid tissue led these authors to review some of the earlier work on changes which occurred in the lymphocyte count in infections or after the injection of bacterial toxins; Dougherty and White [1] concluded that the lymphopenia caused by bacterial toxins was a consequence of the action of adrenal cortex hormones. More recently, however, Lewis and Page [2] cast doubt on this concept when they showed that adrenalectomy does not prevent the decrease in the number of blood lymphocytes which results from the injection of typhoid vaccine. On the other hand, there is histologic evidence that reactions to the injection of bacterial vaccines are associated with the same changes in the adrenal gland as are other forms of stress.[3] In view of these discrepancies, it was considered of

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., and the Department of Medicine, Harvard Medical School, Boston.

1. Dougherty, T. F., and White, A.: Influence of Hormones on Lymphoid Tissue Structure and Function: The Role of the Pituitary Adrenotrophic Hormone in the Regulation of the Lymphocytes and Other Cellular Elements of the Blood, Endocrinology **35**:1, 1944.

2. Lewis, L. A., and Page, I. H.: Changes in Blood Leukocyte Level of Adrenalectomized and Normal Rats Following Administration of Typhoid Vaccine, Am. J. Physiol. **153**:148, 1948.

3. Sayers, G., and Sayers, M. A.: Regulation of Pituitary Adrenocorticotrophic Activity During the Response of the Rat to Acute Stress, Endocrinology **40**:265, 1947. Long, C. N. H.: The Conditions Associated with the Secretion of the Adrenal Cortex, Federation Proc. **6**:461, 1947. Pinchot, G. B.; Close, V. P., and Long, C. N. H.: Adrenal Changes Produced in Rats by Infection with B. Tularense and B. Coli, Endocrinology **45**:135, 1949.

TABLE 1.—*Summary of Changes in Measurements Considered Indicative of Adrenal Cortex Function in Patients Given Typhoid Vaccine Intravenously and Electric Shock in Treatment of Psychoses*

| Experiment No. | Patient | Sex | Age, Yr. | Diagnosis | Day of Study | Rectal Temperature After Vaccine Administration, F. | | Eosinophils per Cu. Mm. Blood | | Lymphocytes per Cu. Mm. Blood | | Urinary Uric Acid Creatinine Ratio | | Therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | At 4 Hr. | Maximal | Initial | % Change | Initial | % Change | Initial | % Rise | |
| 1 | L | F | 37 | Psychoneurosis, reactive depression | 4 | 101.2 | 102.0 | 212 | —89 | 3,515 | —82 | 0.32 | 56 | 1st fever |
| 2 | | | | | 7 | 103.8 | 105.0 | 219 | —80 | 1,510 | —64 | 0.34 | 15 | 2d fever |
| 3 | | | | | 9 | 103.6 | 105.0 | 150 | —71 | 3,305 | —81 | .... | .. | 3d fever |
| 4 | | | | | 12 | 105.0 | 104.0 | 200 | —87 | 4,200 | —82 | 0.36 | 64 | 4th fever |
| 5 | | | | | 14 | 103.4 | 104.0 | 188 | —83 | 4,580 | —82 | 0.35 | 83 | 5th fever |
| 6 | | | | | 25 | 101.6 | 102.4 | 294 | —92 | 4,550 | —82 | 0.31 | 116 | 6th fever |
| 7 | | | | | 27 | 101.0 | 101.0 | 287 | —70 | 3,080 | —84 | 0.33 | 185 | 7th fever |
| 8 | | | | | 29 | 101.6 | 101.8 | 306 | —82 | 3,630 | —92 | 0.34 | 73 | 8th fever |
| 9 | B | F | 39 | Manic-depressive psychosis, depressed | 7 | 102.4 | 102.4 | 175 | —97 | 2,140 | —85 | 0.25 | 0 | 1st fever |
| 10 | | | | | 9 | 100.2 | 100.4 | 219 | —54 | 1,030 | —36 | 0.22 | 86 | 2d fever |
| 11 | | | | | 11 | 100.3 | 100.4 | 300 | —56 | 1,740 | —44 | 0.22 | 50 | 3d fever |
| 12 | | | | | 14 | 100.6 | 100.6 | 212 | —88 | 2,970 | —91 | 0.33 | 21 | 4th fever |
| 13 | | | | | 16 | 100.4 | 100.8 | 225 | —80 | 2,675 | —89 | 0.28 | 29 | 5th fever |
| 14 | | | | | 18 | 100.6 | 100.6 | 281 | —90 | 2,515 | —86 | 0.31 | 71 | 6th fever |
| 15 | | | | | 23 | 100.3 | 100.4 | 212 | —91 | 2,160 | —90 | .... | .. | 7th fever |
| 16 | | | | | 25 | 100.8 | 101.4 | 194 | —89 | 2,940 | —91 | 0.29 | 21 | 8th fever |
| 17 | S | M | 73 | Involutional psychosis—melancholia | 1 | 100.3 | 100.4 | 162 | —88 | 2,880 | —75 | .... | .. | 1st fever |
| 18 | | | | | 3 | 100.6 | 100.8 | 188 | —87 | 2,090 | —97 | .... | .. | 2d fever |
| 19 | | | | | 5 | 100.2 | 100.8 | 112 | —78 | 1,535 | —61 | .... | .. | 3d fever |
| 20 | | | | | 8 | 98.9 | 100.0 | 206 | —91 | 3,075 | —68 | .... | .. | 4th fever |
| 21 | | | | | 10 | 99.8 | 100.2 | 162 | —85 | 3,330 | —65 | .... | .. | 5th fever |
| 22 | | | | | 15 | 99.6 | 99.8 | 238 | —82 | 1,980 | —78 | .... | .. | 7th fever |
| 23 | | | | | 17 | 99.0 | 99.0 | 200 | —81 | 2,930 | —65 | .... | .. | 8th fever |
| 24 | | | | | 22 | 100.2 | 100.2 | 125 | —85 | 1,500 | —84 | .... | .. | 10th fever |
| 25 | | | | | 24 | 99.3 | 99.4 | 134 | —86 | 2,080 | —72 | .... | .. | 11th fever |
| 26 | | | | | 29 | 100.0 | 100.0 | 75 | —71 | 1,860 | —73 | .... | .. | 13th fever |
| 27 | | | | | 31 | 100.1 | 100.2 | 122 | —82 | 1,645 | —53 | .... | .. | 14th fever |
| 28 | | | | | 36 | 99.7 | 99.8 | 112 | —78 | 3,850 | —64 | .... | .. | 16th fever |
| 29 | | | | | 38 | 100.6 | 100.6 | 75 | —92 | 2,110 | —35 | .... | .. | 17th fever |
| 30 | | | | | 42 | ..... | ..... | 144 | —65 | 2,460 | —34 | .... | .. | 2d electric shock |
| 31 | | | | | 44 | ..... | ..... | 116 | —62 | 2,140 | —36 | .... | .. | 3d electric shock |
| 32 | | | | | 46 | ..... | ..... | 138 | —50 | 1,275 | +23 | .... | .. | 4th electric shock |
| 33 | | | | | 49 | ..... | ..... | 219 | —86 | 2,055 | —19 | .... | .. | 5th electric shock |
| 34 | | | | | 56 | ..... | ..... | 156 | —68 | 2,745 | — 3 | .... | .. | (fever due to lung abscess) 6th electric shock |
| 35 | F | M | 19 | Schizophrenia, catatonic | 9 | 101.4 | 101.4 | 150 | —92 | 2,540 | —83 | .... | .. | 1st fever |
| 36 | | | | | 10 | 104.0 | 104.6 | 106 | —97 | 870 | —81 | .... | .. | 2d fever |
| 37 | | | | | 11 | 103.8 | 103.8 | ... | .. | 830 | .. | .... | .. | 3d fever |
| 38 | | | | | 12 | 100.9 | 102.4 | 200 | —78 | 2,120 | —87 | .... | .. | 4th fever |
| 39 | | | | | 14 | 102.4 | 102.6 | 100 | —81 | 2,300 | —87 | .... | .. | 6th fever |
| 40 | | | | | 28 | ..... | ..... | 216 | —33 | 3,210 | —23 | .... | .. | 1st electric shock |
| 41 | | | | | 31 | ..... | ..... | 367 | —56 | 3,205 | —46 | .... | .. | 2d electric shock |
| 42 | | | | | 33 | ..... | ..... | 275 | —34 | 4,180 | —21 | .... | .. | 3d electric shock |
| 43 | R | M | 23 | Schizophrenia, catatonic | 1 | 101.2 | 101.2 | 144 | —65 | 2,140 | —73 | 0.30 | 3 | 1st fever |
| 44 | | | | | 16 | 101.0 | 102.8 | 44 | —70 | 1,805 | —67 | .... | .. | 2d fever |
| 45 | | | | | 19 | 100.0 | 100.0 | 75 | —89 | 2,995 | —79 | .... | .. | 3d fever |
| 46 | | | | | 21 | 100.2 | 100.2 | 75 | —79 | 2,300 | —88 | .... | .. | 4th fever |
| 47 | | | | | 26 | 100.2 | 100.4 | 56 | —66 | 2,830 | —56 | .... | .. | 6th fever |
| 48 | | | | | 28 | 100.6 | 100.6 | 112 | —72 | 3,910 | —92 | .... | .. | 7th fever |
| 49 | | | | | 33 | 99.7 | 100.2 | 56 | —89 | 2,830 | —82 | .... | .. | 9th fever |
| 50 | | | | | 39 | ..... | ..... | 69 | —64 | 2,960 | —29 | .... | .. | 1st electric shock |
| 51 | | | | | 41 | ..... | ..... | 75 | —79 | 2,900 | —14 | .... | .. | 2d electric shock |
| 52 | | | | | 43 | ..... | ..... | 69 | —45 | 2,540 | —21 | .... | .. | 3d electric shock |
| 53 | | | | | 46 | ..... | ..... | 162 | —46 | 3,700 | —34 | .... | .. | 4th electric shock |
| 54 | | | | | 48 | ..... | ..... | 200 | —38 | 3,700 | —32 | .... | .. | 5th electric shock |
| 55 | | | | | 50 | ..... | ..... | 150 | —50 | 3,000 | —31 | .... | .. | 6th electric shock |
| 56 | | | | | 53 | ..... | ..... | 286 | —51 | 3,600 | —26 | .... | .. | 7th electric shock |
| 57 | | | | | 55 | ..... | ..... | 219 | —49 | 3,400 | —11 | .... | .. | 8th electric shock |
| 58 | | | | | 60 | ..... | ..... | 125 | —10 | 2,330 | + 7 | .... | .. | 9th electric shock |
| 59 | H | F | 27 | Schizophrenia, catatonic | 1 | 99.4 | 99.6 | 125 | —90 | 2,200 | —78 | 0.29 | 200 | 1st fever |
| 60 | | | | | 3 | 104.0 | 104.8 | 81 | —69 | 1,130 | —79 | .... | .. | 2d fever |
| 61 | | | | | 5 | 100.1 | 100.2 | 72 | —78 | 1,355 | —54 | .... | .. | 3d fever |
| 62 | | | | | 7 | 100.2 | 100.2 | 69 | —88 | 2,190 | —91 | .... | .. | 4th fever |
| 63 | | | | | 9 | 101.6 | 102.0 | 50 | —88 | 2,185 | —76 | .... | .. | 5th fever |
| 64 | | | | | 13 | ..... | ..... | 25 | +12 | 1,690 | + 6 | .... | .. | 1st electric shock |
| 65 | | | | | 16 | ..... | ..... | 62 | —55 | 2,425 | + 3 | .... | .. | 3d electric shock |
| 66 | | | | | 19 | ..... | ..... | 75 | —67 | 2,440 | —13 | .... | .. | 4th electric shock |
| 67 | | | | | 21 | ..... | ..... | 50 | —50 | 2,560 | — 4 | .... | .. | 5th electric shock |
| 68 | | | | | 23 | ..... | ..... | 56 | —33 | 2,255 | +20 | .... | .. | 6th electric shock |
| 69 | | | | | 28 | ..... | ..... | 63 | —16 | 2,730 | —25 | .... | .. | 8th electric shock |

interest to make studies of the blood leukocytes and of adrenal cortex function in patients who were given typhoid vaccine fever therapy in the treatment of psychoses; comparison of the changes observed with those brought about by electric shock therapy, another type of stress, has been made in the same patients.

## MATERIAL AND METHODS

Observations were made during the course of 69 treatments given to six patients; the diagnoses for the latter varied (table 1). Forty-six of the treatments consisted in the intravenous injection of typhoid vaccine, and the remainder were electric shock treatments given every other day. In many experiments the degree of fever was minimized by the giving of hot drinks or, to one patient, salicylates. Two of the patients, L and B, were well enough after a course of fever therapy to be discharged; the other four, who showed transient or no benefit during treatment with typhoid vaccine, were then given electric shock therapy.

Lymphocyte counts were made, samples of venous blood being used as described previously.[4] Eosinophil counts were made according to the technic described by Forsham and his associates.[5] The method of Folin[6] was used for measuring urinary creatinine, that of Benedict and Franke,[7] after modification, for determination of urinary uric acid and that of Folin and Wu[8] for determination of blood sugar. The urinary output of 17-ketosteroids was measured for each 24 hours, using the method of Callow and his co-workers.[9]

## OBSERVATIONS

*Blood Eosinophils.*—In every patient the number of circulating eosinophils was normal initially and was decidedly diminished four hours after the injection of typhoid vaccine (table 1; fig. 1). The decreases in eosinophils ranged between 54 and 97 per cent and averaged 80 per cent. In two patients (R and H) the control eosinophil counts on days of treatment declined as additional treatments were given, but no such change occurred in the other four patients. No diminution in the lysis

4. Altschule, M. D.; Altschule, L. H., and Tillotson, K. J.: Changes in Leukocytes of the Blood in Man After Electrically Induced Convulsions, Arch. Neurol. & Psychiat. **62**:624 (Nov.) 1949.

5. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15, 1948.

6. Folin, cited in Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 602.

7. Benedict and Franke, cited in Peters and Van Slyke,[6] p. 590.

8. Folin and Wu, cited in Peters and Van Slyke,[6] p. 456.

9. Callow, N. H.; Callow, R. K., and Emmens, C. W.: Colorimetric Determination of Substances Containing the Grouping $-CH_2.CO-$ in Urine Extracts as an Indication of Androgen Content, Biochem. J. **32**:1312, 1938.

of the blood eosinophils after administration of typhoid vaccine occurred in any except during the first week of treatment; the percentage fall in eosinophils with each treatment was as great after the fifth to seventeenth treatments as after the first (table 1; fig. 1). The degree of fever at the time and the severity of the febrile reaction as a whole did not influence the amount of change in these cells.

After electric shock treatments, the changes in blood eosinophil counts ranged from + 12 to — 86 per cent of the control values; the average was — 48 per cent (table 1; fig. 2). The first electric shock treatments after the end of fever therapy were not accompanied with

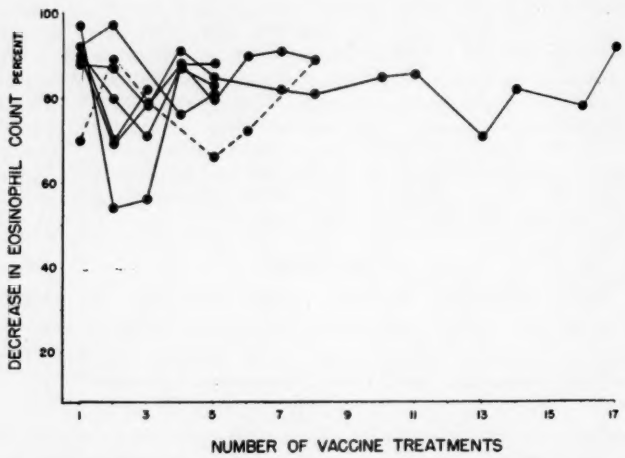


Fig. 1.—Persistent marked decreases in eosinophil counts during course of fever therapy. Broken line indicates values for a patient who had received typhoid vaccine previously.

maximal changes in eosinophil count; in successive treatments the amount of decrease rose and then fell (table 1; fig. 2).

*Blood Lymphocytes.*—The initial lymphocyte counts before the first treatment were normal (table 1). Four hours after the first injection of vaccine the lymphocyte counts decreased by between 73 and 85 per cent (table 1). The counts were still low 24 to 72 hours later and then rose to or above the values noted before the first treatment (table 1; fig. 3). Irrespective of the control count, on the occasion of each injection of vaccine the decreases in lymphocytes ranged between 35 and 92 per cent, averaging 75 per cent. There was a linear relation

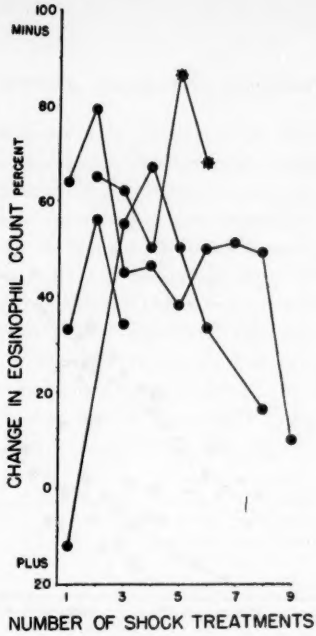


Fig. 2.—Increase in lysis of eosinophils, followed by decrease, during course of electric shock therapy following a succession of fever treatments. The crenated dots indicate values for a patient found to have an abscess of the lung during a period of febrile illness.

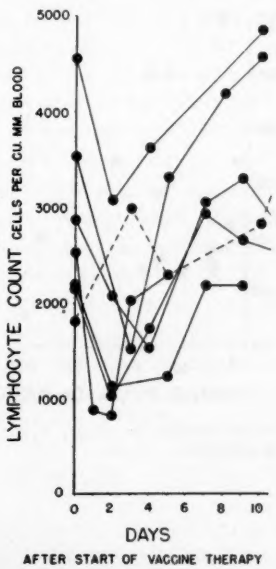


Fig. 3.—Control lymphocyte counts on successive days during the course of fever therapy. Broken line indicates values for a patient who had received typhoid vaccine previously.

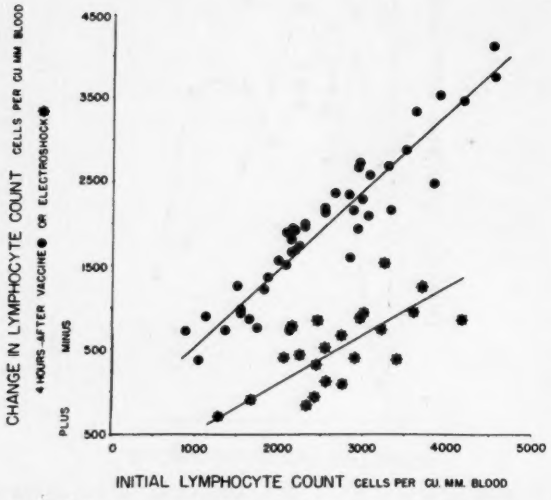


Fig. 4.—Relation of changes in lymphocyte counts to initial lymphocyte counts during fever or electric shock treatments.

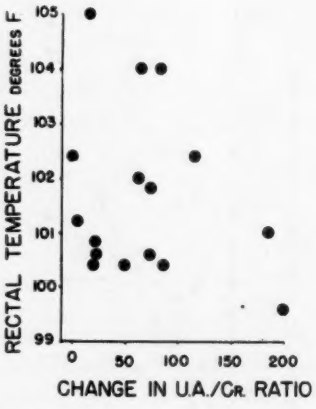


Fig. 5.—Relation between increases in urinary uric acid to creatinine ratio (U.A./Cr.) and rectal temperature.

between the initial lymphocyte count and the amount of decrease in circulating lymphocytes at each treatment with typhoid vaccine (fig. 4).

During the course of electric shock therapy the control counts did not vary consistently before successive treatments (table 1). Four hours after treatment the lymphocyte counts showed changes of between + 23 and — 46 per cent, with an average of — 16 per cent (table 1; fig. 4); the largest changes occurred during the initial treatments, with progressively smaller changes thereafter. Here, too, a linear relation was demonstrated between the initial count at each treatment and the amount of decrease in circulating lymphocytes (fig. 4). However, for a given lymphocyte count the decreases were much smaller than after the injection of typhoid vaccine (table 2; fig. 4).

TABLE 2.—*Percentage Decreases in Lymphocytes*

| | Decreases in Lymphocytes, %, Resulting from | | |
|---|---|---|---|
| No. of Treatments | Fever Therapy | Electric Shock Therapy | Electric Shock Therapy After a Course of Fever Therapy |
| 1 to 2 | 75 | 47 | 23 |
| 3 to 5 | 76 | 33 | 14 |
| 6 to 9 | 82 | 23 | 19 |

*Urinary Uric Acid to Creatinine Ratio.*—The ratio before injection of the vaccine ranged between 0.22 and 0.36 (table 1). In 11 of 16 studies it rose impressively (table 1; fig. 5). In one patient studied extensively, the amount of change in the ratio was greater in the later studies, when the degree of fever was minimized (table 1). There was an inverse relation between the elevation in temperature and the amount of change in ratio (table 1; fig. 5).

*Dextrose Tolerance.*—The dextrose tolerance curves showed high peaks before treatment. No significant change in the fasting blood sugar level or in dextrose tolerance occurred as a consequence of the repeated induction of fever (fig. 6).

*Excretion of 17-Ketosteroids.*—The excretion of 17-ketosteroids was in the normal range before treatment. During the early part of the period of fever therapy a rise above the control levels occurred in one patient, followed by slight fall subsequently (fig. 7). In one patient many low values were observed (L, fig. 7); a periodic variation was apparent, with two cycles a month, although no menstrual periods occurred during the time of study.

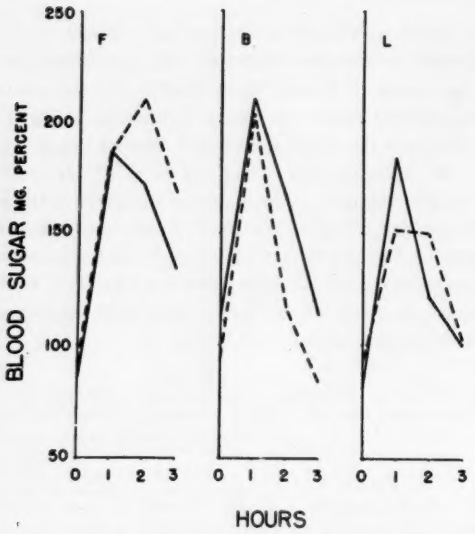


Fig. 6.—Changes in blood sugar in patients F, B and L after administration of 100 Gm. of dextrose orally. Solid line indicates values before any treatment and broken line values after end of a course of fever therapy.

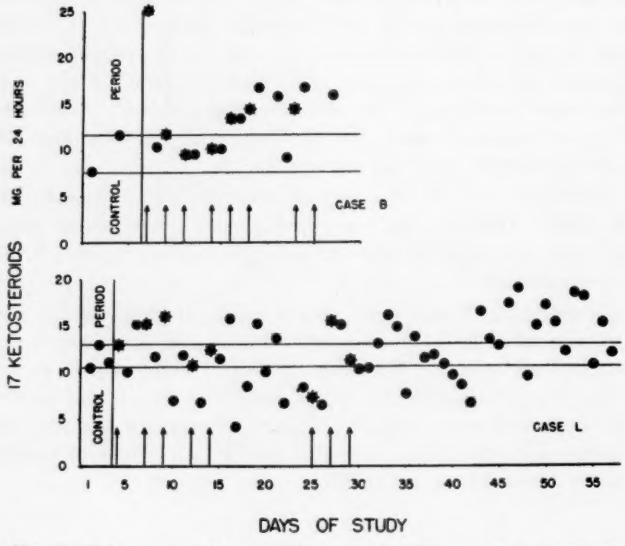


Fig. 7.—Urinary excretion of 17-ketosteroids. The crenated dots indicate values on days in which fever treatments were given.

COMMENT

Interpretation of the results of the present study is difficult, for it appears that several different processes act simultaneously during a febrile reaction following the injection of typhoid vaccine. It has been known for many years that injection of typhoid vaccine or bacterial protein lowers the lymphocyte count [10]; other bacterial proteins may have the same effect when injected.[11] In addition, it was first shown many years ago,[12] and subsequently confirmed, that the blood eosinophil count also falls as a consequence of the injection of bacterial proteins [13]; clinicians have long been aware of the fact that eosinophils commonly disappear from the blood during the course of a number of febrile illnesses in man. Dougherty and White [1] ascribed the changes in lymphocytes described by many of the observers cited above to the action of adrenal cortex hormones. It is apparent, however, that other factors also operate, for adrenalectomy does not completely prevent lympholysis after the injection of typhoid vaccine in animals.[2] Some workers have

10. (*a*) Lewis and Page.[2] (*b*) Scully, F. J.: The Reaction After Intravenous Injections of Foreign Protein, J. A. M. A. **69**:20 (July 7) 1917. (*c*) Cowie, D. M., and Calhoun, H.: Nonspecific Therapy in Arthritis and Infections: A Study of the Changes in the Blood Consequent on the Intravenous Injection of Typhoid Protein; a Consideration of the Analogy Between the Typhoid Paroxysm and the Malarial Paroxysm, Arch. Int. Med. **23**:69 (Jan.) 1919. (*d*) Robertson, R. C., and Yu, H.: Leucopenia and the Toxic Substances of B. Typhosus, J. Hyg. **38**:301, 1938. (*e*) Smith, E. V. D.: The Effect of Injections of Toxic Extracts of the Typhoid Bacillus on the Blood Picture in Rabbits, Am. J. Hyg., Sect. B **29**:15, 1939. (*f*) Morgan, H. R.: Immunologic Properties of an Antigenic Material Isolated from Eberthella Typhosa, J. Immunol. **41**:161, 1941. (*g*) Favorite, G. O., and Morgan, H. R.: Effects Produced by the Intravenous Injection in Man of a Toxic Antigenic Material Derived from Eberthella Typhosa: Clinical, Hematological, Chemical and Serological Studies, J. Clin. Investigation **21**:589, 1942. (*h*) Favorite, G. O., and Morgan, H. R.: Therapeutic Induction of Fever and Leukocytosis Using a Purified Typhoid Pyrogen, J. Lab. & Clin. Med. **31**:672, 1946.

11. (*a*) Live, J. I.; Stubbs, E. L., and Mackey, W. L.: The Influence of Intracutaneous Injection of Sonic Filtrate of Brucella Abortus on the Blood-Leukocyte Picture in Cattle Positive to Brucellosis, J. Infect. Dis. **75**:170, 1944. (*b*) Hendershott, R. A., and Johnston, C. B.: The Value of Blood Examinations in the Diagnosis of Bovine Tuberculosis, Proceedings of the United States Live Stock Sanitary Association, 1941, p. 157. (*c*) Feldman, W. H., and Stasney, J.: Leukenoid Response of Tuberculous Rabbits to Administration of Tuberculin, Am. J. M. Sc. **193**:28, 1937. (*d*) Stasney, J., and Feldman, W. H.: The Character of the Leukocytic Response to Tuberculin in Sensitized Calves, ibid. **195**:20, 1938. (*e*) Chambers, W. W.; Koenig, H.; Koenig, R., and Windle, W. F.: Site of Action in the Central Nervous System of a Bacterial Pyrogen, Am. J. Physiol. **159**:209, 1949.

12. Simon, C. E.: A Contribution to the Study of Eosinophilia, Internat. Clin. **1**:166, 1906.

13. Scully.[10b] Hendershott and Johnston.[11b]

shown that the fall in blood lymphocyte count [11a-d] and eosinophil count [11b] after the injection of tuberculin or of a protein derived from Bacillus abortus (Brucella abortus) occurs only in those animals with tuberculosis or sensitization to the protein, respectively. It is doubtful, however, that a similar immunologic phenomenon was a factor in the present study, since all the patients in whom observations were made showed the changes and had not been immunized or sensitized to the organisms injected. This finding, however, does not rule out the presence of other immunologic factors in some of the phenomena to be discussed below. The question also arises whether or not the decreases in lymphocyte and eosinophil counts seen here might be part of a general toxic leukopenic process. Against this concept is the fact that the lymphopenic factor is separable from the granulopenic effect, as was shown by Smith [10e] and by Dennis and Senekjian [14]; moreover, in the present study the granulocytes always increased after the injection of the vaccine, usually by 50 to 200 per cent.

Comparison in the same patients of changes in lymphocyte counts obtained after the injection of typhoid vaccine with those observed after electric shock treatment shows the latter to be much smaller than the former. It is to be noted, however, that the lympholytic response after electric shock treatments is smaller in patients given electric shock after a course of fever therapy than in other patients who received no antecedent fever therapy (table 2). Even when this is taken into account, the lympholytic response during each fever treatment is much greater than after electric shocks. Moreover, the pattern of change seen in the course of the two types of treatment is quite different. The percentage fall in lymphocytes after typhoid vaccine therapy showed no tendency to vary; on the other hand, after electric shock therapy given subsequent to the fever treatments, progressive diminution in the degree of lympholytic response occurred as the number of electric shocks increased, in a manner parallel to that seen with electric shock therapy given without antecedent fever treatments (table 2). The fact that patients given electric shock treatment after a course of fever therapy showed a smaller lympholytic response than those who did not have antecedent fever therapy is probably significant; patients given six to nine electric shock treatments without previous fever therapy exhibited an average decrease in lymphocytes of 23 per cent, which is similar to the showing of patients given their initial electric shocks a few days after having had six to 17 (average, nine) fever treatments. Fever therapy, therefore, causes a depression of the lympholytic response to electric shock treatments in a manner similar to that of other forms of stress. It appears likely that the decrease in lymphocyte count seen after each

14. Dennis, E. W., and Senekjian, H.: A Leukocidal Toxin Extracted from Typhoid Bacilla, Am. J. Hyg., Sect. B **30**:103, 1939.

fever treatment is the consequence of two factors: (1) the factor of activity of adrenal cortex steroid hormones and (2) a factor, presumably toxic, which causes the greater part of the change observed, and which increases in degree with repeated fever treatments, masking the effects of the action of the adrenal cortex.

Another change in lymphocytes apparent during the course of fever therapy but not during electric shock treatment was the persistently low count which was seen for 24 to 72 hours only after the first fever treatment and which was not associated with loss of the lympholytic response to fever treatments given during this period (table 1; fig. 3). The explanation for this phenomenon may be related to the observations of a number of workers who have shown [15] that when foreign proteins are injected into animals there is necrosis of lymph nodes, followed after approximately three days by conspicuous proliferation of the germinal centers; the latter change is accompanied with an increase in antibody titers in the blood. Presumably, if this necrosis occurred after the first injection of typhoid vaccine in man also, the supplying of lymphocytes to the circulation by the lymph nodes would be retarded, so that the lymphocyte count would remain low; the lymphocytes in the circulation would still respond in the normal manner in terms of percentages to subsequent injections of the toxins. Subsequently, as immunity developed and the germinal centers became hyperplastic, a supply of lymphocytes would become available to restore the counts to normal values within a matter of hours after the effects of each injection of typhoid vaccine wore off. It is of interest that the only patient who did not show persistent lowering of the lymphocyte count after the first injection of the vaccine was the one who had been given typhoid vaccine previously (R, table 1 and fig. 3).

The changes in eosinophil count which occurred during the fever treatments also were greater than those seen after electric shock treatments. The pattern of change likewise was different in the two, a large percentage fall occurring after each fever treatment, even up to the seventeenth, while the eosinophil response decreased during the later

15. Hellman, T., and White, G.: Das Verhalten des lymphatischen Gewebes während eines Immunisierungsprozesses, Virchows Arch. f. path. Anat. **278**:221, 1930. Wiseman, B. K.: The Induction of Lymphocytosis and Lymphatic Hyperplasia by Means of Parenterally Administered Protein, J. Exper. Med. **53**:499, 1931. Ehrich, W., and Voigt, W.: Ueber die Reaktionen des Gefässbindegewebsapparates auf intravenöse Staphylokokkeninjektionen und ihre Bedeutung, Beitr. z. path. Anat. u.z. allg. Path. **93**:348, 1934. Rich, A. R.: Acute Splenic Tumor Produced by Non-Bacterial Antigens, Proc. Soc. Exper. Biol. & Med. **32**:1349, 1935. Conway, E. A.: Reaction of Lymphatic Tissue in Early Stages of Bacterium Monocytogenes Infection, Arch. Path. **25**:200 (Feb.) 1938. Ehrich, W. C., and Harris, T. N.: The Formation of Antibodies in the Popliteal Lymph Node in Rabbits, J. Exper. Med. **76**:335, 1942.

electric shock treatments in a manner similar to that observed previously in patients given electric shock without antecedent fever therapy [16]; the reason for the fact that the eosinophilolytic response was initially small and increased during the first few electric shock treatments given after the course of fever therapy is not immediately apparent. At any rate, the differences in the pattern of the changes seen suggests that different mechanisms in the main determine the changes in eosinophil counts after fever therapy and after electric shock treatments.

The results of the studies of the urinary uric acid to creatinine ratio made here also differed in some respects from the changes seen after electric shock; in the case of the latter initial treatments caused notable increases in the ratio, with a decline in this response as the electric shock treatments continued.[16] No such pattern of change occurred in the course of typhoid vaccine therapy; here the only relation observed was an inverse one between temperature and increase in the urinary uric acid to creatinine ratio. It is not clear why this difference occurred; the effects of the fever per se on metabolic processes and renal function, and of dehydration in the studies in which fever rose to high levels, should be among the factors considered as possible causes of the differences noted.

The excretion of 17-ketosteroids was normal in both patients studied before treatment, in agreement with the observations of Escamilla [17] in psychotic persons. During the course of fever therapy changes occurred in one patient which resembled those pictured by Forbes and her collaborators [18] as taking place in nonpsychotic patients during episodes of fever caused by malaria or by the injection of typhoid vaccine; these changes consisted in the occurrence of an initial increase with some subsequent fall. It is possible that in this patient (B) the findings were modified by the fact that the patient, anorectic while psychotic, began to eat well soon after therapy was started. The effect of variations in caloric intake on 17-ketosteroid excretion has been discussed by Landau and his associates.[19] One of the patients, L., showed a cyclic change in the output of 17-ketosteroids, with peaks every 15 days, although she had

16. Altschule, M. D., and Parkhurst, B. H.: Effect of Treatment on Excretion of 17-Ketosteroids in Patients with Mental Disease, Arch. Neurol. & Psychiat., to be published.

17. Escamilla, R. F.: Diagnostic Significances of Urinary Hormonal Assays: Report of Experience with Measurements of 17-Ketosteroids and Follicle Stimulating Hormone in the Urine, Ann. Int. Med. **30**:249, 1949.

18. Forbes, A. P.; Donaldson, E. C.; Reifenstein, E. C., Jr., and Albright, F.: The Effect of Trauma and Disease on the Urinary 17-Ketosteroid Excretion in Man, J. Clin. Endocrinol. **7**:264, 1947.

19. Landau, R. L.; Knowlton, K.; Anderson, D.; Brandt, M. B., and Kenyon, A. T.: The Effect of Starvation on Urinary 17-Ketosteroid Excretion, J. Clin. Endocrinol. **8**:133, 1948.

no menstrual periods. Similar observations have been made in another young psychotic woman who was not having menstrual periods.[16]

It appears valid to conclude that changes in adrenal cortex function occur during the course of reactions following the intravenous injection of typhoid vaccine and that these changes resemble those seen in other types of stress. Indeed, experiments on animals given coli or typhoid vaccines have been reported [8] in which the histologic changes associated with stress were seen in the adrenal cortex. The adrenal cortex changes described by Olitzki and his co-workers [20] in animals given bacterial proteins are difficult to relate to those seen in the present work, for the animals in these experiments were almost certainly deep in shock, as indicated by profound hypothermia. Similarly, the observations of workers who studied adrenal cortex cholesterol in animals or patients who died of infections [21] are difficult to relate to those in the present investigation.

Although it seems evident that the changes in adrenal cortex function caused by the injection of bacterial vaccines are similar to that caused by other types of stress, it is clear that the indexes used to measure these changes in man are greatly influenced by other factors which are toxic and possibly immunologic in nature; accordingly, a true estimate of the degree of stress caused by such injections is difficult to attain. A corollary of this conclusion is that changes in lymphocyte and eosinophil counts need not always indicate the occurrence of, or reflect the degree of, change in adrenal cortex function. The use of the urinary uric acid to creatinine ratio is also subject to reservations under the conditions of the present study.

The possibility must be considered that some of the change encountered in the present study was part of the adrenal reaction to heat described by Conn and his co-workers.[22] Against this concept is the fact that the higher levels of internal temperature attained had no effect in enhancing the cytologic and chemical changes observed in the present

20. Olitzki, L.; Avinery, S., and Koch, P. K.: The Hypothermic and Adrenohaemorrhagic Effects of Bacterial Vaccines, J. Immunol. **45**:237, 1942. Olitzki, L.; Czaczkes, J. W., and Kuzenok, A.: Endotoxic Factors of Rickettsia Prowazeki and Their Immunological Relationship to the Endotoxins of Other Gram Negative Microorganisms, ibid. **53**:365, 1946. Tal, C., and Olitzki, L.: The Toxic and Antigenic Properties of Fractions Prepared from the Complete Antigen of Shigella Dysenteriae, ibid. **58**:337, 1948.

21. Sayers, G.; Sayers, M. A.; Fry, E. G.; White, A., and Long, C. N. H.: The Effect of the Adrenotrophic Hormone of the Anterior Pituitary on the Cholesterol Content of the Adrenals, with a Review of the Literature on Adrenal Cholesterol, Yale J. Biol. & Med. **16**:361, 1944.

22. Conn, J. W.; Johnston, M. W., and Lewis, L. H.: Acclimatization to Humid Heat: A Function of Adrenal Cortical Activity, J. Clin. Investigation **25**:912, 1946.

study. The fact is established[23] that the hypothalamus governs the cardiovascular and respiratory mechanisms in the endogenous febrile reaction. It is possible also that activation of the hypothalamus during the febrile reaction results in stimulation of the anterior lobe of the pituitary gland by means of the mechanisms described by Cheng and his colleagues[24] and by Hume[25]; stimulation of the adrenal cortex would then follow, even though the rise in body temperature was minimized by measures favoring peripheral vasodilatation.

## SUMMARY AND CONCLUSIONS

Observations on changes in blood leukocyte counts and in other measurements considered to be indexes of adrenal cortex function have been made in patients given typhoid vaccine intravenously in the treatment of psychoses. Lymphocytes and eosinophils in the blood decreased greatly in number during each treatment. The degree of elevation in temperature which occurred had no detectable effect on the amount of change in the lymphocyte or eosinophil counts. Analysis of the changes which occurred favors the concept that two groups of factors, one adrenocortical and the other toxic and immunologic, operate; the effects of the latter overshadow those of the former. Changes in the urinary uric acid to creatinine ratio varied inversely as the degree of fever. The observations indicate that changes in blood leukocytes and in urinary uric acid excretion should not always be interpreted as accurate indexes of adrenal cortex function. The excretion of 17-ketosteroids followed the pattern seen in other types of stress. Typhoid vaccine fever therapy causes an initial stimulation of the adrenal cortex and then a later depression in its reactivity.

23. Jona, J. L.: A Contribution to the Experimental Study of Fever, J. Hyg. **15**:169, 1915. Ranson, S. W., Jr.; Clark, G., and Magoun, H. W.: The Effect of Hypothalamic Lesions on Fever Induced by Intravenous Injection of Typhoid-Paratyphoid Vaccine, J. Lab. & Clin. Med. **25**:160, 1939.

24. Cheng, C. P.; Sayers, G.; Goodman, L. S., and Swinyard, C. A.: Discharge of Adrenocorticotrophic Hormone in the Absence of Neural Connections Between the Pituitary and Hypothalamus, Am. J. Physiol. **158**:45, 1949.

25. Hume, D. M., and Wittenstein, G. J.: The Relationship of the Hypothalamus to Pituitary-Adrenocortical Function, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950.

# SERUM ESTERIFIED FATTY ACIDS WITH FAT TOLERANCE TESTS IN DIABETES MELLITUS

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LIPEMIA and acetonuria, in patients with diabetes mellitus, for many years have been regarded as evidence of disturbed fat metabolism. Summaries [1] with additional studies have been published.

According to Bloor, Gillette and James, the lipemia in controlled diabetes can be small, but high values occur in the moderately severe disease and the blood lipids in some subjects are remarkably increased. These authors fed 100 cc. quantities of olive oil emulsified in acacia to dogs and determined postprandial lipemia curves. Then nine tenths of the pancreas was removed, and after wound healing the experiments were repeated. The postabsorptive level of the blood lipids in these diabetic dogs increased even to the stage of serum opalescence. The glycerides were increased the most, cholesterol next and lecithin the least. With a standard meal these diabetic dogs also had an increased lipemia, again mainly of the glycerides, with cholesterol following and lecithin changed the least. Bloor, Gillette and James concluded that a high fasting level of blood lipids, especially of the glyceride fraction, is characteristic of severe diabetes. Allen considered the diabetic lipemia a secondary disturbance of fat metabolism for which high glycosuria and hyperglycemia are necessary prerequisites. He stated that persons having mild or severe diabetes with glycosuria, when controlled by diet, have no remarkable lipemia regardless of the intake of fat. The

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1. Bloor, W. R.; Gillette, E. M., and James, M. S.: Fat Metabolism in Diabetes: I. The Blood Lipids in Experimental Diabetes, J. Biol. Chem. **75**:61, 1927. Allen, F. M.: Experimental Studies in Diabetes, J. M. Research **1**:219, 1922. Gray, H.: Lipoids in 1,000 Diabetic Bloods, with Special Regard to Prognosis, Am. J. M. Sc. **168**:35, 1924.

blood lipids in diabetes, according to Gray, show regular increases equal to those of the blood sugar, and diabetics with blood lipids of less than 1 Gm. per 100 cc. live longer than those with a higher value.

Chaikoff, Smyth and Gibbs [2] reported that the blood lipid fractions of diabetic children under insulin and diet control are within the normal range. They observed no relation between the serum cholesterol level and the severity of the diabetes, or with acidosis. The cholesterol content of the blood, they stated, is not a reliable index of control in diabetes. The fatty acid values fluctuated widely, an indication that this is a much more labile fraction the fluctuations of which have not been thoroughly correlated with the various phases of the disease. Gibbs and Chaikoff [3] demonstrated that the hyperlipemia of the diabetic dog is due mainly to an increase in triglycerides, with little or no increase of the cholesterol and phosphatide fractions. Curtis and Sheldon [4] observed a correlation between acidosis and an increase of the blood lipids and noted a decrease of the blood lipids when the diabetes was controlled, regardless of the amount of fat ingested as food. They concluded that the lipemia of the diabetic occurs when carbohydrate combustion is diminished to the level where acidosis is produced and that the inability to oxidize fat causes the lipemia.

According to these published statements, lipemia occurs with diabetes mellitus in patients and in animals made diabetic by removal of a large amount of the pancreas. The precise relationship between the lipemic state and the diabetic disease is not clearly established. However, there is general agreement that the triglyceride fraction (fatty acids) is the main constituent of the lipemic state and the one with the greatest range of fluctuation. This fraction, in clinical practice, has not been measured because simple procedures for analysis have not been available. Therefore, the level of cholesterol in the blood has been assumed by some to be a fairly accurate index of the total lipid content, despite published statements to the contrary.

Blotner [5] gave a test meal of 500 cc. of 20 per cent cream to 21 diabetics and used the plasma cholesterol content as an index for the total blood fat concentration. The obese diabetic had a higher fasting cholesterol value than the normal obese person. In patients with insulin

2. Chaikoff, I. L.; Smyth, F. S., and Gibbs, G. E.: The Blood Lipids of Diabetic Children, J. Clin. Investigation **15**:527, 1936.

3. Gibbs, G. E., and Chaikoff, I. L.: Lipid Metabolism in Experimental Pancreatic Diabetes: I. Blood and Liver Lipids of Dogs Fasted During Total Insulin Deprivation, Endocrinology **29**:877, 1941.

4. Curtis, A. C., and Sheldon, J.: The Effect of Ingested Fat and Acidosis upon the Hyperlipemia of Diabetes Mellitus, J. Clin. Investigation **11**:829, 1932.

5. Blotner, H.: Tolerance Tests in Diabetes Mellitus, in Medical Papers Dedicated to Henry Ashbury Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, Inc., 1936, p. 450.

treatment Blotner observed a greater rise in the cholesterol of the blood following the test meal than in those without insulin. The nonobese diabetics without insulin had a higher fasting cholesterol level than the normal persons, and the cholesterol level of the plasma after the meal remained unchanged during eight hours. The nonobese diabetics with insulin treatment had a lower fasting cholesterol value than those without insulin, and after the test meal the cholesterol level gradually decreased during the eight hours of the test. These results failed to reveal a lipemic state in the diabetic after a test meal, largely because the lipid measured (cholesterol) was not the kind fed (triglyceride). Published reports stating that the level of cholesterol in the blood can be taken as an index of the total lipids of the blood are, therefore, misleading. They assume that the individual constituents of the lipid fraction of the blood remain in the same proportion as they are at the so-called fasting level, regardless of the intake of food fat, which is largely triglycerides. This assumption, as demonstrated especially by experiments in diabetic dogs, is incorrect. The chief reason for this indirect evaluation of the total serum lipids is the lack of a simple clinical method for the estimation of the esterified fatty acids of the serum, comparable with the one used for the estimation of the cholesterol content.

Bauer and Hirsch [6] recently described a colorimetric method for estimating the total esterified fatty acids in human serums. In another publication they [7] reported the levels of these fatty acids, as determined by their method, in the serum of 102 presumably healthy human adults. The blood samples were obtained before breakfast from men and women who had taken no food since the preceding evening. The maximum level of the esterified fatty acids was 12.6, the minimum was 7.0 and the mean was 9.2 milliequivalents per liter of serum. This method was then used in an investigation of the variations in the level of the esterified fatty acids of the serum in healthy human adults and in diabetics after the ingestion of a standard meal of fats.

Studies of the lipid content of the blood following a test meal of fat have been made by others. Hiller, Linder, Lundsgaard and Van Slyke [8] used a test meal of 1 Gm. of butter for each kilogram of body weight. They observed after the test meal a greater increase in the plasma fatty acids and lecithin of nephritic patients with initially high blood lipids than in normal subjects or nephritics without persistent lipemia. No

6. Bauer, F. C., Jr., and Hirsch, E. F.: A New Method for the Colorimetric Determination of the Total Esterified Fatty Acids in Human Sera, Arch. Biochem. **20**:242, 1949.

7. Bauer, F. C., Jr., and Hirsch, E. F.: Esterified Fatty Acid Levels of Normal Human Sera, Arch. Biochem. **23**:137, 1949.

8. Hiller, A.; Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: Fat Metabolism in Nephritis, J. Exper. Med. **9**:931, 1924.

changes occurred in the cholesterol content of the plasma. Man and Gildea [9] reported a pronounced rise in the fatty acids of the human serum following the ingestion of large amounts of fat. The test meal contained unsalted butter, 40 per cent cream, two or three slices of toast and a cup of coffee, but no sugar. Each test subject received 3.5 to 4 Gm. of fat for each kilogram of body weight. The serum fatty acids increased notably above the initial fasting level; the average was 62 per cent; the maximum was 133 per cent, and the minimum was 34 per cent. In six subjects the maximum level was reached in four hours and in three after six hours. Man and Gildea also studied the effect on the serum fatty acids of a standard balanced meal containing 0.5 to 1.0 Gm. of fat per kilogram of body weight. With one exception this meal also caused an appreciable increase in the serum fatty acids, the average increase being 21 per cent and the maximum 40 per cent. Accordingly, the ingestion of other food with the fat does not prevent the rise in serum fatty acids. Chaikoff, McGavack and Kaplan [10] gave 100 cc. quantities of olive oil flavored with oil of spearmint to seven young adults after a 10 to 14 hour fast. They observed great individual variations in the fatty acid content of the blood, estimated at two hour intervals during a 10-hour period. The maximum increase observed was 35 per cent.

### FAT TOLERANCE TEST IN HEALTHY ADULTS

A fat meal consisting of 36 per cent cream (the largest portion), unsalted butter, bacon, water-packed fruit, gluten bread and coffee, but no sugar, in the amounts of 2 or 3 Gm. of fat per kilogram of body weight was selected. The subject was given this test meal in the morning, about 14 hours after the meal of the evening before. At 8:00 a.m. the first sample of blood was drawn, and between 8:00 and 9:00 a.m. the test meal was eaten. Seven samples of blood were drawn thereafter at intervals of one hour while the subject was at rest. The total esterified fatty acid levels of the serum were determined by the method described by Bauer and Hirsch.[6] The total cholesterol content of these samples was determined by the colorimetric method for blood analysis,[11] adapted to the spectrophotometer. Twenty-eight tests were made on 21 subjects (table 1). Of these 28 tests, 18 were with 3 Gm. of fat per kilogram of body weight and 10 were with 2 Gm. of fat per kilogram of body weight.

9. Man, E. B., and Gildea, E. F.: The Effect of Ingestion of Large Amount of Fat and a Balanced Meal on Blood Lipids of Normal Man, J. Biol. Chem. **99**:61, 1932.

10. Chaikoff, I. L.; McGavack, T. H., and Kaplan, A.: Blood Lipids in Post-Absorptive State and After Ingestion of Fat in Normal Subjects and in a Case of Disseminated Cutaneous Xanthomata, J. Clin. Investigation **13**:1, 1934.

11. Sackett, G. E.: Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum, J. Biol. Chem. **64**:203, 1925.

## RESULTS

The serum fatty acids in healthy human beings increased appreciably following a meal containing 2 or 3 Gm. of fat per kilogram of body weight. The increment of increase was not the same nor was it reached within the same time in the various persons tested; also, the increase was greater in the same person with the 3 Gm. per kilogram ratio than

TABLE 1.—*Results of Twenty-Eight Fat Test Meals Given Twenty-One Normal Subjects*

| Sex * | Body Weight, Kg. | Gm. Fat Given per Kg. | Esterified Fatty Acids in mEq./L. of Serum | | |
|---|---|---|---|---|---|
| | | | Initial Level | Maximum Level | Per Cent Increase |
| M | 90.9 | 3 | 10.7 | 26.3 | 146 |
| | .... | 2 | 8.5 | 17.3 | 104 |
| F | 56.9 | 3 | 8.6 | 20.0 | 132 |
| F | 67.3 | 3 | 10.7 | 23.6 | 125 |
| | .... | 2 | 10.8 | 17.8 | 64 |
| F | 63.6 | 3 | 7.3 | 15.1 | 107 |
| F | 56.9 | 3 | 7.1 | 13.5 | 89 |
| | .... | 2 | 9.7 | 13.4 | 37 |
| M | 70.0 | 3 | 9.7 | 18.4 | 88 |
| F | 45.4 | 3 | 9.6 | 17.8 | 86 |
| F | 68.2 | 3 | 8.6 | 15.9 | 85 |
| | .... | 2 | 9.3 | 15.9 | 71 |
| F | 52.3 | 3 | 8.6 | 15.9 | 84 |
| F | 47.7 | 3 | 8.7 | 15.1 | 74 |
| F | 61.8 | 3 | 8.8 | 14.2 | 61 |
| | .... | 2 | 8.3 | 12.3 | 49 |
| F | 77.3 | 2 | 8.8 | 14.0 | 59 |
| F | 55.5 | 3 | 7.9 | 12.2 | 54 |
| F | 61.8 | 3 | 7.4 | 11.4 | 54 |
| | .... | 2 | 7.7 | 11.0 | 42 |
| F | 61.8 | 2 | 10.3 | 15.5 | 50 |
| F | 63.6 | 3 | 7.4 | 10.8 | 46 |
| F | 48.1 | 3 | 10.6 | 15.1 | 42 |
| F | 61.8 | 2 | 8.3 | 11.7 | 42 |
| F | 70.5 | 3 | 7.9 | 10.7 | 35 |
| | .... | 3 | 7.7 | 9.6 | 24 |
| F | 54.5 | 2 | 8.7 | 11.7 | 34 |
| F | 53.6 | 3 | 10.3 | 12.9 | 25 |

* Ages were from 19 to 35 years.

with the 2 Gm. per kilogram ratio. After the maximum level of increase was reached, the serum fatty acids declined toward the initial level. When placed in a graph, the levels of the serum fatty acid measured at intervals of an hour after a test meal formed a curve (fig. 1). The peak level of the serum fatty acids was reached usually by the third to fourth hour after the meal was taken. Among the 28 tests completed, the maximum level of the serum fatty acids in 10 was reached in three hours, in another 10 in four hours, in four by the second hour, in three by the fifth hour and in one within one hour. The initial serum fatty acid levels found in 21 subjects on the 28 tests ranged between 7.1 and 10.8,

and averaged 8.8, milliequivalents per liter of serum. The value of the initial fatty acid level of the blood established a quantum used as a reference in computing individual percentages of increase. This initial value represents only the level of departure under the conditions of the experiment, not necessarily the lowest level possible to which the serum fatty acids could fall after a longer period without food. In a subject on whom data are not listed who was kept without food for several days, the initial fatty acid content of the serum was much below the minimal range given.

The individual maximum level in 18 tests on 17 subjects ranged from 9.6 to 26.3 milliequivalents per liter of serum fatty acids with a

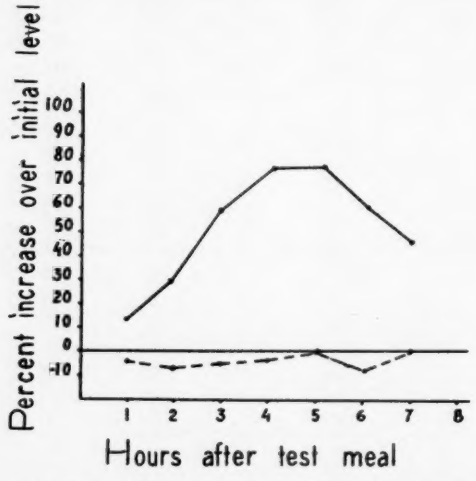


Fig. 1.—Graph illustrating the rise and decline of the serum esterified fatty acids (solid line) and the inconsequential change of the total serum cholesterol (dotted line) following a standard fat test meal in a healthy adult. The base line was 8.7 milliequivalents per liter of esterified fatty acids and 7.3 milliequivalents per liter (or 283 mg. per 100 cc.) of total cholesterol.

ratio of 3 Gm. of fat per kilogram, and in 10 tests on 10 subjects the level ranged from 11.00 to 17.8 milliequivalents with a ratio of 2 Gm. of fat per kilogram. When the individual percentage increases from minimum to maximum in the 28 tests were grouped, results of five tests on four subjects showed increases of between 104 and 146. The maximum percentage increase was in a subject who with a test meal of 2 Gm. of fat per kilogram of body weight had a 104 per cent increase. Another in this group with a 125 per cent increase on the 3 Gm. per kilogram meal had a 64 per cent elevation with the 2 Gm. per kilogram meal.

In seven tests on six subjects the individual percentage increases ranged between 71 and 89; one of these subjects (showing an 85 per cent increase on the 3 Gm. meal) on the 2 Gm. per kilogram test meal had a 71 per cent increase, and another (showing an 89 per cent increase on the 3 Gm. meal) with the smaller fat meal had only a 37 per cent increase.

The individual percentage increases in the remaining 14 tests on 11 subjects ranged between 24 and 61. Three of the 14 tests (with 59, 42 and 34 per cent increases) were with meals containing 2 Gm. of fat per kilogram of body weight. One of these subjects, who from her physical build would be thought able to gain weight easily, had only a 24 and a 35 per cent increase with two tests using the 3 Gm. per kilogram test meal.

The total cholesterol values of the serums determined with each analysis for esterified fatty acids were remarkably unchanged after all the test meals, fluctuating within a narrow range, slightly more or even less than the value determined in the first (fasting) sample of each experiment. This clearly indicates that the total cholesterol levels of the blood do not parallel the total lipid content, and accordingly, total cholesterol values do not provide an index for the total serum lipid values.

The level of lipemia produced in human subjects by a standard fat meal (exogenous fat) has wide individual variations. The separation of the percentage increases into three groups, of course, is entirely arbitrary in this series of 28 studies. A larger series doubtless would have some increases in the gaps between the first and second and between the second and third groups. However, the sampling in this study has disclosed among apparently healthy adults subjects with marked, intermediate and moderate elevations of the serum fatty acids (lipemia) following a test meal of fat. In physical build the ones with the large percentage increase were invariably persons tending to be obese and who easily gained weight—the weight gainers. Several persons in the upper levels of the middle group were of similar build, but one in the middle group with a 74 per cent elevation was decidedly spare, and one in the lowest percentage group on two tests (showing a 35 and a 24 per cent increase) had a physical build resembling that of persons in the first group.

## COMMENT

According to Frazer's [12] review, only the changes which occur in fat within the first few hours have significance in its absorption from the intestine. With an excessive amount of fat intake in the human being,

12. Frazer, A. C.: The Absorption of Triglyceride Fat from the Intestine. Physiol. Rev. **26**:103, 1946.

the peak of absorption is reached in about six hours. With normal amounts, such as 30 Gm., the maximum systemic lipemia occurs in two or three hours and the blood fat levels return to normal within 4½ hours. The significant interval for intestinal lipolysis in either case is less than six hours. The initial phases of lipolysis are rapid, but the rate soon declines, and the process stops before 30 per cent of the contained fatty acids have been liberated. Regardless of the volume of the substrate, the percentage remains the same. Fatty acids form water-soluble and diffusible complexes with bile salts. Frazer was of the opinion that a significant amount of fat is absorbed as unhydrolyzed or partially hydrolyzed triglyceride. The precise way in which it passes through the outer border of the intestinal cell is not known, but emulsification to 0.5 micron particulate size is important. He also stated that probably at least 60 per cent of the long chain triglyceride fat absorbed may pass through the outer membrane of the intestinal cell as finely dispersed particles of unhydrolyzed fat. Most of the test meals used in studies of this kind have a large content of triglyceride fat. The fat in the usual diets also is largely of this chemical composition.

Factors influencing absorption in the intestine and the removal of the fat material from the blood after absorption are important. Frazer's review of the knowledge of the absorption of triglyceride fats by the intestine stated that there are two main hypotheses concerning the mechanism of this physiologic process: (1) the lipolytic and (2) the partitional. There is general agreement on the main changes which fat may undergo during absorption, such as emulsification, hydrolysis and phosphorylation, as well as on the recognition of the importance of the bile salts and the activity of the adrenal cortex in this physiologic process. The differences rest in the way these changes are accomplished and in the level of their importance in absorption. The changes of the fat in the intestinal lumen are (1) emulsification and (2) hydrolysis. The $p_H$ of the intestinal content is at about 6.5; the only emulsifying system found effective in a $p_H$ range of 6.0 to 8.5, according to Frazer, is the triple combination of fatty acid, bile salt and monoglyceride. The emulsified fats in the intestinal lumen are fatty acids and triglycerides, diglycerides and monoglycerides. The flocculation pattern of the intestinal emulsion is that of negatively charged particles. Emulsification, thus, (*a*) may provide an increased interfacial area for subsequent hydrolysis or (*b*) may facilitate the absorption of finely dispersed unhydrolyzed fat.

The postprandial lipemia, therefore, has at least two determining elements: (1) the speed and the amount of fat absorption from the intestinal lumen and (2) the rate at which the lipid particles enter and are removed from the blood stream. Schmidt's [13] review of the extrahepatic

13. Schmidt, C. L. A.: The Extrahepatic Function of Bile, Physiol. Rev. **7**:129, 1927.

function of bile stated that when the flow of bile to the intestine is stopped a marked decrease in the absorption of fat occurs. He remarked that Bidder and Schmidt as early as 1852 had stated this clearly. Patients with hepatic disease associated with decreased bile output accordingly could have decreased fat absorption, hence a smaller increase of serum fatty acids following a meal of fat.

The lipids of the blood are dispersed in finely divided globules. Frazer and Stewart [14] examined the ultramicroscopic particles, so-called blood dust, in the human blood and concluded that they are mainly particles of fat and seem to carry a negative electric charge. The lipemia after a fat meal, as determined by their study, appeared within 1¼ hours, attained a maximum in two to three hours and returned to the resting level in 4½ hours. Absorption of fat and removal from the blood, thus, are physiologic processes, balanced or unbalanced depending on which phase is dominant. These studies, however, so far as is now known, pertain only to physiologic processes concerned with the lipemia occurring with absorption of food fat. The removal of particles of small dimension from the blood stream by the reticuloendothelial system of the tissues is well known, and studies of injected emulsified lipid [15] indicate that removal of these particles is also accomplished by phagocytosis.

Wertheimer and Shapiro [16] stated that the nature of the fat deposited in adipose tissues is determined by the balance of the fat in the diet, the fat synthesized in the body and the fat broken down in metabolism. Animals feeding largely on carbohydrates deposit a fat specific to the species because most fat is synthesized within the body. Only on ingestion of large amounts of specific fat is the depot fat altered so that it approaches the composition of fat fed. Apparently, no studies have been made distinguishing the so-called exogenous from the endogenous forms of lipemia. These comments indicate simply some of the basic physiologic problems involved in studies of the lipemias.

## FAT TOLERANCE TESTS IN DIABETICS [17]

The test meal containing 3 Gm. of fat per kilogram of body weight was given to 21 diabetic patients, and analyses of the esterified fatty acids, cholesterol and sugar of the blood were made as outlined. The diabetes of 13 of these patients was classified as mild and that of eight

14. Frazer, A. C., and Stewart, H. C.: Ultramicroscopic Particles in Normal Human Blood, J. Physiol. **90**:18, 1937.

15. Hirsch, E. F., and Weinhouse, S.: Role of Fixed Tissue Phagocytes in Lipid Metabolism, Arch. Path. **30**:1079 (Nov.) 1940.

16. Wertheimer, E., and Shapiro, B.: The Physiology of Adipose Tissue, Physiol. Rev. **28**:451, 1948.

17. These diabetic patients came to us for the fat tolerance tests from the Morton Clinic of St. Luke's Hospital, through the courtesy of Drs. Carl A. Hedblom, Jerry I. Newman and B. P. Phibbs.

as severe. The essential portions of the results of the analyses of the blood are in tables 2 and 3. They disclose significant differences from the results observed with the group of 21 normal adults.

TABLE 2.—*Results of Fat Test Meal (3 Gm. of Fat per Kilogram of Body Weight) Given Thirteen Mildly Diabetic Patients*

| Sex | Esterified Fatty Acids in mEq./L. of Serum | | | Total Serum Cholesterol, Mg./100 Cc. | | Blood Sugar, Mg./100 Cc. | |
|---|---|---|---|---|---|---|---|
| | Initial Level | Maximum Level | Per Cent Increase | Initial Level | Range | Initial Level | Range |
| | | | | Without Insulin | | | |
| F | 8.0 | 15.5 | 94 | 267 | 260 to 283 | 101 | 86 to 110 |
| M | 10.3 | 20.0 | 94 | 267 | 260 to 275 | 146 | 177 to 220 |
| F | 11.0 | 20.0 | 82 | 215 | 215 to 244 | 142 | 128 to 131 |
| F | 15.3 | 58.10 | 280 | 283 | 260 to 300 | 138 | 142 to 163 |
| | 14.3 | 35.2 | 152 | 291 | 291 to 317 | 150 | 146 to 177 |
| | | | | Insulin Used But None Taken Before Test Meal | | | |
| M | 10.0 | 25.6 | 156 | 215 | 215 to 238 | 89 | 94 to 108 |
| F | 12.2 | 16.4 | 34 | 238 | 222 to 244 | 117 | 121 to 159 |
| F | 8.4 | 13.7 | 63 | 308 | 275 to 308 | 138 | 134 to 188 |
| F | 12.1 | 32.2 | 166 | 304 | 291 to 308 | 104 | 97 to 121 |
| F | 11.7 | 18.4 | 56 | 230 | 215 to 238 | 131 | 128 to 159 |
| F | 14.0 | 19.7 | 41 | 365 | 335 to 355 | 138 | 154 to 227 |
| | | | | Insulin Taken Before Test Meal | | | |
| F | 12.5 | 24.3 | 94 | 244 | 230 to 244 | 182 | 163 to 220 |
| F | 12.5 | 26.4 | 111 | 275 | 267 to 283 | 243 | 177 to 285 |
| F | 7.0 | 11.8 | 69 | 275 | 260 to 291 | 50 | 52 to 84 |

TABLE 3.—*Results of Fat Test Meal (3 Gm. of Fat per Kilogram of Body Weight) Given Eight Patients with Severe Diabetes*

| Sex | Esterified Fatty Acids in mEq./L. of Serum | | | Total Serum Cholesterol, Mg./100 Cc. | | Blood Sugar, Mg./100 Cc. | |
|---|---|---|---|---|---|---|---|
| | Initial Level | Maximum Level | Per Cent Increase | Initial Level | Range | Initial Level | Range |
| | | | | Insulin Used But None Taken Before Test Meal | | | |
| F | 14.3 | 29.1 | 104 | 251 | 238 to 267 | 300 | 216 to 300 |
| F | 14.6 | 35.2 | 142 | 308 | 267 to 317 | 194 | 189 to 243 |
| F | 13.7 | 22.9 | 67 | 365 | 365 to 395 | 63 | 128 to 188 |
| F | 13.4 | 21.8 | 62 | 355 | 365 to 395 | 79 | 163 to 273 |
| F | 13.7 | 28.7 | 109 | 308 | 291 to 317 | 253 | 263 to 300 |
| F | 11.4 | 27.1 | 137 | 418 | 385 to 430 | 138 | 138 to 182 |
| F | 16.4 | 20.7 | 26 | 267 | 251 to 283 | 400 | 388 to 400 |
| | | | | Insulin Taken Before Test Meal | | | |
| F | 37.5 | 80.0 | 113 | 467 | 442 to 508 | 206 | 235 to 273 |

In the group of the 13 persons with clinically mild diabetes, with or without insulin control, the fasting serum fatty acid levels tended to be in the high normal range, and the peak level attained ranged into the high levels observed in the first group of the normal adults. Five in this group of diabetics had peak levels much above or equal to the maxi-

mum levels observed in the normal persons. Another significant difference from the normal is in the contour of the curve (fig. 2) by which the amount and duration of the postprandial lipemia are graphically represented. In mild diabetes the peak level of the lipemia consistently

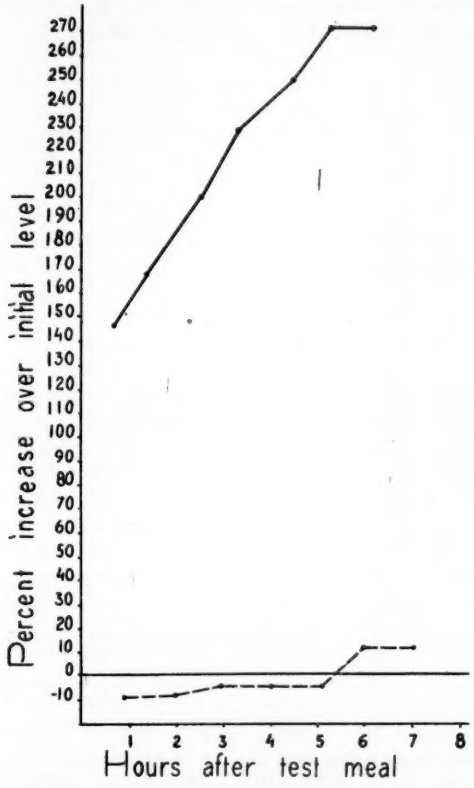


Fig. 2.—Graph illustrating the prolonged elevation of the serum esterified fatty acids (solid line) following a standard fat test meal in a patient with mild diabetes. No significant changes occurred in the cholesterol content (dotted line) of the serum. The base line was 12.1 milliequivalents of esterified fatty acids per liter and 7.8 milliequivalents per liter (or 302 mg. per 100 cc.) of total cholesterol.

was later; in other words, the duration of the lipemia was prolonged, in several tests attaining the maximum near or at the end of seven hours (or even longer). The cholesterol levels in all tests on these diabetic

patients did not follow the lipemia (fatty acid) curves and, in fact, had no significant variations from the initial level. The initial level of the cholesterol of the serum indicated simply the approximate level at which the results of other determinations would fall.

The results in the group of 8 patients with severe diabetes, all using insulin, disclosed a postprandial (fat test meal) lipemia similar to but severer than that observed in the group with mild diabetes. The initial

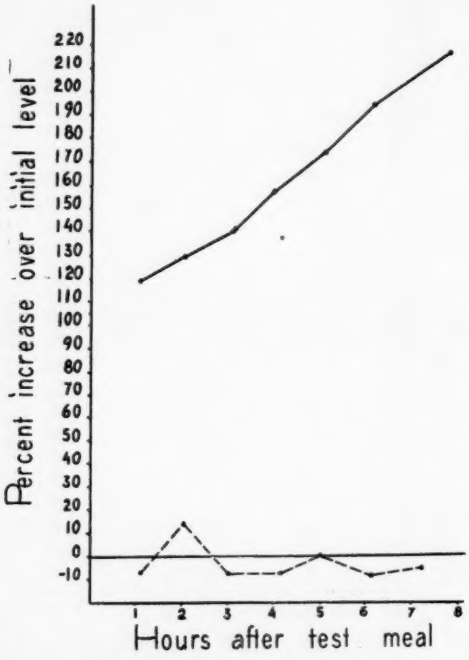


Fig. 3.—Graph illustrating the high initial value of the serum esterified fatty acids (solid line) and the notable prolonged rise of these lipids following a standard fat test meal in a patient with severe diabetes. No significant changes occurred in the total cholesterol content (dotted line) of the serum. The base line was 37.5 milliequivalents per liter of esterified fatty acids and 12.1 milliequivalents per liter (or 468 mg. per 100 cc.) of total cholesterol.

fasting fatty acid level in those with severe diabetes was above the highest initial values observed in the normal group; in fact, it equaled or even exceeded many of the maximum postprandial levels observed in the normal group. The serum fatty acids in the patients with severe diabetes reached maximum levels several or even many times that attained

in the normal group, and as in the patients with mild diabetes the postprandial peak of the serum fatty acids was reached after six or seven hours, or even longer. Accordingly, the postprandial phase of lipemia was prolonged, and the percentage increase over the initial high level was large (fig. 3). Again, in this group the initial value of the total serum cholesterol indicated simply the general level which obtained during the test meal analyses. The individual analyses of total cholesterol in each fat tolerance test gave no indication of the lipemia demonstrated by the analyses of the fatty acid content of the serum. Sugar determinations of the blood failed to disclose any correlation with the postprandial increase of the serum fatty acids in diabetes.

## SUMMARY

The esterified fatty acid content of the lipemia which followed the ingestion of a fat meal in the amounts of 2 or 3 Gm. of fat per kilogram of body weight was determined by a new spectrophotometric method at hourly intervals for seven hours in 21 healthy human adults (28 tests) and in 21 diabetic patients. Simultaneous analyses of serum cholesterol, and in the diabetics also of blood sugar, were made.

The percentage increase of the serum fatty acids above the initial so-called fasting level among the normal adults ranged in five tests between 104 and 146, in seven tests between 71 and 89 and in 16 tests between 24 and 64. The total cholesterol content of the serum varied only slightly from the initial value in each test. Accordingly, the cholesterol content of the serum is not an index of the total lipid content of the serum. The amount of postprandial lipemia varies in individual persons, and among healthy adults are those with marked, intermediate and smaller elevations of the serum fatty acids following a test meal of fat. The peak level of the serum fatty acids in health is reached usually by the third to the fourth hour after the test meal. Among 13 persons with clinically mild diabetes, with or without insulin control, the initial, so-called fasting level of the serum fatty acids was in the high range of this level for healthy adults, and the peak level following the test meal ranged into the highest levels observed for the normal group. However, the maximum of the serum fatty acids in the postprandial lipemia of the persons with mild diabetes was attained later than in the normal adults. The duration of the postprandial lipemia, therefore, was longer. The cholesterol content of the serum in these persons with mild diabetes had no significant variations from the initial level.

Eight patients with severe diabetes, all using insulin, had a similar but more pronounced increase of the serum fatty acids following the fat test meal. The initial serum fatty acid content was above the highest initial values observed in the normal group, and even exceeded the maximum postprandial level of several. The maximum level was attained

late and was several or even many times that of the healthy group. In diabetes, accordingly, the postprandial phase of lipemia is prolonged and the percentage increase over the initial, also elevated, level is large. The cholesterol analyses in each fat tolerance test gave no indication of the postprandial lipemia which the quantitative analyses of the serum fatty acids disclosed. The sugar level of the blood likewise had no correlation with the rise of the serum fatty acids.

The quantitative spectrophotometric method for the analysis of the serum esterified fatty acids provides a convenient clinical facility for the estimation of this important and labile fraction of the blood lipids in health and disease.

# ADULT RENAL OSTEITIS FIBROSA WITH METASTATIC CALCIFICATION AND HYPERPLASIA OF ONE PARATHYROID GLAND

## Report of a Case

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LONG-STANDING renal disease with accompanying hyperplasia of the parathyroid glands and osteitis fibrosa is a rare syndrome which only in recent years has been adequately described from the clinical and pathologic viewpoints with at least partial clarification of the pathogenesis. Because of its unusually interesting clinical and pathologic features, particularly in children, the disorder has formed the basis of a number of reports dealing with young persons. It is not appreciated so well, however, that a similar syndrome may occur in the adult.

Lucas [1] in 1883 first noted the association of albuminuria and rickets, and Fletcher [2] in 1911 described skeletal changes in children with long-standing renal dysfunction. The condition has subsequently been described under various designations, such as renal rickets and renal dwarfism. These children showed either decrease or cessation of growth, with skeletal deformities and enlargement of the bones at the endochondral junctions. Because of the similarity of these lesions to those of rickets, especially on roentgenologic examination,[3] the term "renal rickets" was coined and is still widely used. It is now known

From the Departments of Pathology and Orthopaedics of the Research and Educational Hospitals and the University of Illinois College of Medicine.

1. Lucas, R. C.: On a Form of Late Rickets Associated with Albuminuria, Rickets of Adolescence, Lancet **1**:993, 1883.

2. Fletcher, H. M.: Case of Infantilism with Polyuria and Chronic Renal Disease, Proc. Roy. Soc. Med. **4**:95, 1911.

3. Parsons, L. G.: The Bone Changes Occurring in Renal and Coeliac Infantilism, and Their Relation to Rickets: I. Renal Rickets, Arch. Dis. Childhood **2**:1, 1927.

that this condition is not the result of a vitamin D deficiency, and, therefore, the term "rickets" should be considered as inappropriate.[4] The earlier literature on the subject was reviewed in 1930 by Mitchell,[5] who gave details on the renal and osseous changes in a large series of cases. It is noteworthy that the parathyroid glands were not mentioned in this review, although in 1920 Bergstrand,[6] in a study of 10 cases of renal disease associated with parathyroid enlargement, had given indication of the close relation of the parathyroids and the kidneys. Cases in which enlargement of the parathyroid glands was coexistent with osseous lesions and renal disease were subsequently reported.[7] It then became apparent that renal rickets and renal hyperparathyroidism were probably the same condition. Indeed, cases first reported as renal rickets have been considered as renal hyperparathyroidism by later observers, and the reverse has also been true.[8]

It has been shown that adults are not immune to these lesions, although they are more rarely affected because endochondral bone formation has ceased and because in most cases renal insufficiency in adults becomes incompatible with life before parathyroid and skeletal lesions have time to develop fully. Albright, Drake and Sulkowitch[9] in 1937 first drew attention to the rare combination in an adult of renal insufficiency, chronic acidosis, hyperplasia of the parathyroid glands, skeletal lesions identical with those of hyperparathyroidism and metastatic calcifications, which in their opinion deserved consideration as an entity. Although a few similar cases of adults and children had been

4. Park, E. A., and Elliot, M. M.: Renal Hyperparathyroidism with Osteoporosis (Osteitis) Fibrosa Cystica, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 29, p. 7.

5. Mitchell, A. G.: Nephrosclerosis (Chronic Interstitial Nephritis) in Childhood, with Specific Reference to Renal Rickets, Am. J. Dis. Child. **40**:101 (July); 345 (Aug.) 1930.

6. Bergstrand, H.: Parathyreoideastudien: II. Ueber Tumoren und hyperplastische Zustände der Nebenschilddrüsen, Acta med. Scandinav. **54**:539, 1920-1921.

7. (*a*) Hubbard, R. S., and Wentworth, J. A.: A Case of Metastatic Calcification Associated with Chronic Nephritis and Hyperplasia of the Parathyroids, Proc. Soc. Exper. Biol. & Med. **18**:307, 1921. (*b*) Smyth, F. S., and Goldman, L.: Renal Rickets with Metastatic Calcification and Parathyroid Dysfunction, Am. J. Dis. Child. **48**:596 (Sept.) 1934. (*c*) Langmead, F. S., and Orr, J. W.: Renal Rickets Associated with Parathyroid Hyperplasia, Arch. Dis. Childhood **8**:265, 1933.

8. Anderson, W. A. D.: Hyperparathyroidism and Renal Disease. Arch. Path. **27**:753 (April) 1939.

9. Albright, F.; Drake, T. G., and Sulkowitch, H. W.: Renal Osteitis Fibrosa Cystica, Bull. Johns Hopkins Hosp. **60**:377, 1937.

previously described,[10] this was the first complete report. Herbert, Miller and Richardson [11] in 1941 collected 14 cases from the literature and added one of their own.

In our review of the literature we found a total of 17 cases (table 1) which could be included as examples of this syndrome. Eleven cases are of adults and six of children. Only one case of a child less than 12 years of age was recorded. Only two of the listed case reports did not mention hyperplasia of the parathyroids; in one [12] a basophilic adenoma of the pituitary was present, and the parathyroids could not be found at autopsy, while in the other,[10c] that of a 2 year old child, the parathyroids were said to be normal but no further description was given. In the present case there was the unique situation of hyperplasia affecting one parathyroid gland to such a degree that it was palpable on physical examination. This has not, to our knowledge, been described previously. Also, in our case a striking degree of bronzing of the skin was present. In addition, a congenital type of renal lesion was noted, with long-standing renal insufficiency, osteitis fibrosis and metastatic calcifications of the subcutaneous tissues and the medium-sized arteries. Regression of the metastatic calcifications during life is a remarkable feature of this case. For these reasons it is felt that a report of this case is warranted.

## REPORT OF CASE

A 27 year old white machinist entered the Orthopaedic Service of the University of Illinois Research and Educational Hospitals on Dec. 27, 1946 because of pain, weakness and inability to walk. He had considered himself to be reasonably well until a year before his admission, when he first noticed swelling of the ankles, pains in the right groin and thigh and masses in the lower part of the right leg and in the right inguinal region. Roentgenograms revealed foci of calcification in the masses of the right leg. The pain increased despite therapy, and three months before his admission the patient was forced to avoid any weight bearing on or motion of the right thigh and leg. At that time also a nonpainful and nontender swelling appeared rapidly over the upper one third of the outer portion of the right forearm. This swelling extended down to the wrist. It slowly diminished in size. Six weeks prior to entry a mass rapidly developed between the shoulders. This swelling decreased, but at the time of admission a noticeable enlargement of each medial scapular region was still present.

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10. (*a*) Hubbard and Wentworth.[7a] (*b*) Smyth and Goldman.[7b] (*c*) Lightwood, R.: A Case of Dwarfism and Calcinosis Associated with Widespread Arterial Degeneration, Arch. Dis. Childhood **7**:193, 1932. (*d*) Castleman, B., and Mallory, T. B.: The Pathology of the Parathyroid Gland in Hyperparathyroidism: A Study of 25 Cases, Am. J. Path. **11**:1, 1935.

11. Herbert, F. K.; Miller, H. G., and Richardson, G. O.: Chronic Renal Disease, Secondary Parathyroid Hyperplasia, Decalcification of Bone, and Metastatic Calcification, J. Path. & Bact. **53**:175, 1941.

12. Brown, C. L., and Ginsberg, I. W.: Osteoporosis Associated with Extensive Metastatic Calcification and Chronic Renal Disease, Arch. Path. **30**:108 (July) 1940.

TABLE 1.—*Summary of Reported Cases of Renal Disease with Parathyroid Hyperplasia and Osteitis Fibrosa*

| Case No. | Authors | Age, Yr. | Sex | Autopsy | Renal Lesion | Parathyroids | Bone | Metastatic Calcifications | Description of Skin |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Albright and others [9]..... | 45 | M | Yes | Chronic nephritis | 4 enlarged; total wt., 11 Gm.; largest gland weighed 5 Gm. | Osteitis fibrosa generalisata | Subcutaneous; arteries | Sallow |
| 2 | Hubbard and Wentworth [7a].. | 20 | M | Yes | Interstitial nephritis | 2 large glands (small adenoma in 1) | Osteitis fibrosa | Subcutaneous; arteries; heart | Not described |
| 3 | Smyth and Goldman [7b]..... | 14 | M | Yes | Hydronephrosis and hydroureter | 5 hyperplastic glands: 0.5 × 0.4 × 0.3 to 1.4 × 0.7 × 0.7 cm. | Osteoporosis | Subcutaneous; heart; lungs; arteries | Lemon-yellow |
| 4 | Lightwood [10c] ..... | 2 | F | Yes | Chronic glomerulo-nephritis | 1 normal parathyroid | Osteosclerosis and osteoporosis | Arteries; trachea; heart; lung | Yellow-tan |
| 5 | Castleman and Mallory [10d].. | 25 | M | Yes | Chronic pyelonephritis | 0.9 × 0.7 × 0.3 cm.; 1.7 × 0.8 × 0.5 cm.; 1.0 × 0.8 × 0.4 cm.; 1 gland normal | Bone cysts | Subcutaneous; arteries | Not described |
| 6 | Herbert and others [11]..... | 40 | F | Yes | Renal hypoplasia | 960 mg.; 580 mg.; 820 mg.; 2,850 mg. | Osteoporosis | Arteries; periarticular | Slight icteric tinge |
| 7 | Brown and Ginsburg [12]..... | 55 | M | Yes | Chronic glomerulo-nephritis | Basophilic adenoma of pituitary; no parathyroid glands found | General decalcification; bone cysts | Arteries; trachea; bronchi; heart | Pallid and dry |
| 8 | Castleman and Mallory [23b].. | 45 | M | Yes | Chronic glomerulo-nephritis | 4 Gm.; 3 Gm.; 2 Gm.; 2 Gm. | Decalcification | Arteries; periarticular | Not described |
| 9 | Magnus and Scott [25b]..... | 23 | F | Yes | Chronic nephritis | 3,270 mg.; 840 mg.; 1,510 mg. | Osteoporosis | Subcutaneous; arteries; heart | Yellowish |
| 10 | Bass and Pakter [37]..... | 12 | F | No | Congenital poly cystic kidneys | ..... | ..... | Subcutaneous; arteries | Yellowish |
| 11 | Shelling and Remsen [42]..... | 17 | M | Yes | Hydronephrosis | 4 enlarged glands | Osteoporosis | Arteries | Pigmented |
| 12 | Platt, R., and Owen, T. K.: Lancet **2**: 135, 1934 | 18 | M | Yes | Chronic nephritis | Normal | "Erosion of bone" | Subcutaneous; arteries | Pigmented |
| 13 | Pollack, H., and Siegal, S.: J. Mt. Sinai Hosp. **2**: 270, 1936 | 41 | F | Yes | Chronic nephritis | Hyperplasia of 3 glands | No gross disease | Subcutaneous; arteries; lungs | Yellow-brown |
| 14 | Curtis, L. E., and Feller, A. E.: Ann. Int. Med. **17**: 1005, 1942 | 40 | M | Yes | Chronic nephritis | 1 large gland | Osteoporosis | Periarticular; lungs; brain; pancreas | Many brown-black pigmented areas |
| 15 | Soffer, L. J., and Cohn, C.: Arch. Int. Med. **71**: 639 (May) 1943 (case 8) | 18 | F | Yes | Chronic nephritis | 4 hyperplastic glands | Osteoporosis | Subcutaneous; arteries; lungs; stomach | Not described |
| 16 | Wigley, J. E. M., and Hunter, D.: Proc. Roy. Soc. Med. **38**: 141, 1945 | 21 | F | Yes | Chronic nephritis | 4 hyperplastic glands | Not described | Subcutaneous; arteries | Pale |
| 17 | Burkholder, T. M., and Braund, R. R.: J. Urol. **57**: 1001, 1947 | 46 | M | Limited to kidneys | Polycystic kidneys | ..... | No changes on roentgenogram | Subcutaneous; arteries | Pale and sallow |
| 18 | Dreskin and Fox..... | 27 | M | Yes | Megaloureter and hydronephrosis | Predominant hyperplasia of 1 gland; remainder hyperplastic | Healing osteitis fibrosa generalisata | Subcutaneous; arteries | Bronze |

There had been a weight loss of 64 pounds (29 Kg.) in the previous year. The skin was said to have always been deeply pigmented. Mild dyspnea on exertion and edema of the ankles had been noted since the onset of symptoms. The patient had had polyuria with nocturia, but there had been no dysuria or hematuria. No history of scarlet fever or of rheumatic fever was obtained.

At the age of 6 years he had had an illness considered to be "kidney disease." At the age of 17 years albumin had been demonstrated in the urine, and on repeated subsequent tests albuminuria was present. Ten years prior to admission calculi had been removed from the submaxillary gland ducts. For 1½ years before entry the wife noticed that the patient exhibited spasmodic muscular contractions when asleep or at rest.

*Results of Physical Examination.*—Examination revealed a well developed white man who appeared weak but not acutely ill. The skin was brown and diffusely pigmented, but the oral mucous membrane was normal. The pupils were constricted,

TABLE 2.—*Laboratory Determinations*

| Date | Urine | RBC, Millions per Cu. Mm. | NPN, Mg. per 100 Ml. | Urea Nitrogen, Mg. per 100 Ml. | Creatine, Mg. per 100 Ml. | $CO_2$ Volumes per Cent | Ca, Mg. per 100 Ml. | Inorganic Phosphate, Mg. per 100 Ml. | Phosphatase, Bodansky Units | A/G, Gm. per 100 Ml. | Cholesterol, Mg. per 100 Ml. | Cholesterol Esters, Mg. per 100 Ml. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12/30 | Sp. gr., 1.005 | 2.91 | 108 | 81 | 5.5 | 34 | 10.4 | 8.7 | 6.7 | 4.7/2.0 | 265 | 227 |
| 1/ 7 | +++ albumin | 2.88 | 68 | .. | 8.4 | .. | .... | ... | ... | ..... | ... | ... |
| | +++ albumin | | | | | | .... | ... | ... | ..... | ... | ... |
| 1/ 8 | + Ca | 3.61 | .. | .. | ... | .. | 9.1 | 7.3 | ... | ..... | 199 | 166 |
| 1/13 | .... | .... | .. | .. | ... | .. | 11.5 | 7.2 | 8.9 | 5.0/2.4 | ... | ... |
| Removal of Parathyroid Tumor | | | | | | | | | | | | |
| 1/21 | +++ albumin | .... | .. | .. | ... | .. | 4.3 | 8.4 | 6.4 | ..... | ... | ... |
| 1/22 | .... | .... | .. | .. | ... | .. | 5.6 | 7.4 | 19.4 | ..... | ... | ... |
| 1/27 | .... | .... | .. | .. | ... | .. | 4.5 | 7.3 | 20.2 | ..... | ... | ... |
| 1/28 | .... | .... | 69 | .. | 9.5 | .. | 4.7 | 5.9 | 13.4 | 3.8/2.7 | ... | ... |
| 2/ 6 | .... | 3.3 | .. | .. | ... | .. | 5.4 | 5.5 | 12.0 | ..... | ... | ... |
| 3/ 8 | .... | .... | 97 | .. | ... | .. | 6.1 | 6.2 | 4.5 | ..... | ... | ... |
| 4/16 | .... | 3.4 | .. | .. | ... | .. | 6.2 | 7.2 | 22.2 | ..... | 298 | 192 |
| Second Admission | | | | | | | | | | | | |
| 6/11 | +++ albumin | 2.95 | 166 | 150 | 20.0 | .. | 4.7 | 16.2 | 12.9 | 6.0/2.5 | ... | ... |
| 6/20 | + Ca | .... | 288 | 119.5 | 16.0 | .. | 4.5 | 10.9 | 16.6 | ..... | ... | ... |
| 6/21 | .... | .... | 248 | .. | 23.5 | .. | 4.2 | 15.2 | 8.2 | ..... | ... | ... |

but the fundi were normal. The teeth were white, and there were no signs of caries. The thyroid gland was not palpable. The heart and lungs were clear to auscultation and percussion. The blood pressure was 116/44. The abdomen was essentially normal. The genitalia were those of a normal male, except that the pubic hair had a feminine distribution. The muscles of the arms and legs were somewhat atrophic. Numerous dense, hard subcutaneous plaques and nodules were palpated. These plaques were prominent along the lateral and medial aspects of the legs, on the right forearm just below the elbow and in the right thenar web. The trapezius muscles were greatly enlarged, and the swellings here seemed to be fibrous in character. The radial arteries were stiff and hard.

*Laboratory Findings* (on first admission).—The specific gravity of the urine was 1.005, with a 2+ reaction for albumin. The sediment showed occasional pus cells. There were 8 Gm. of hemoglobin per 100 ml. of blood, 2,900,000 red blood cells and 13,800 white blood cells per cubic millimeter, with 47 per cent neutrophils, 46 per cent lymphocytes, 6 per cent eosinophils and 1 per cent monocytes. The hematocrit was 25 and the sedimentation rate (corrected) 24 mm. per hour. Total protein measured 6.7 Gm. per 100 ml., with 4.7 Gm. of albumin and 2.0 Gm. of globulin. The carbon dioxide-combining power was 34 volumes per cent.

Nonprotein nitrogen was 103 mg., calcium 10.4 mg. and inorganic phosphorus 8.7 mg., per 100 ml. The Wassermann and Kahn reactions were negative. (See table 2 for further laboratory data.)

*Clinical Course.*—Three days after his admission the patient complained of a painful swelling of the interphalangeal joint of the left index finger. Relief followed the administration of salicylates. Results of a Mosenthal test indicated considerable

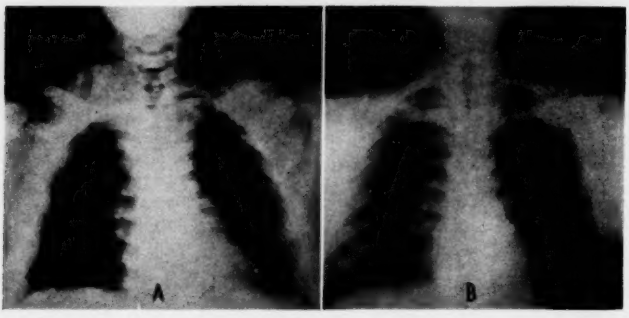


Fig. 1.—*A*, large subcutaneous calcifications overlying scapular areas posteriorly are clearly seen. *B*, roentgenogram made three months following resection of parathyroid nodule. Soft tissue calcifications in scapular areas have completely disappeared.

Fig. 2.—*A*, calcium deposits outline course of digital arteries. Soft tissue calcification in space between second and third metacarpals is prominent. In the proximal end of the third metacarpal is a cystic area. End of distal phalanx of first finger has virtually disappeared. *B*, soft tissue calcifications have almost completely dissolved three months following resection of parathyroid nodule, although arterial calcifications remain unchanged. Cyst in metacarpal bone is less evident but still present. Recalcification of terminal phalanx has taken place.

impairment of renal concentration. Roentgenographic examinations (figs. 1 *A* and 2 *A*) revealed calcification of blood vessel walls throughout the body, multiple irregular calcified areas in the soft tissues of the lower extremities and irregular

calcium deposits in the soft tissue of the hands. Huge nodular calcifications were seen in the supraclavicular and infraclavicular regions. There was a small cystic area occupying the head of the third left metacarpal. The appearance of the calvarium was mottled, with thickening of the skull anteriorly. The kidneys were not visualized after intravenous injection of iodopyracet (diodrast®). A fracture with deformity of the right femoral neck was noted. Roentgenograms of the chest showed clear pulmonary fields and a normal cardiac shadow.

The patient was seen in consultation by members of the Medical Service, and at this examination a mass was noted in the region of the lower pole of the thyroid on the left. This region was explored about two weeks after his admission. Although it was intended that only enough tissue be removed for histologic diagnosis, virtually the entire mass was excised because incision of the capsule resulted in the rolling out of soft tan tissue. The specimen received in the department of pathology consisted of a roughly ovoid mass of pink-yellow tissue, measuring 3.5 by 2.5 by 2 cm. The surface was finely granular and the tissue soft and friable.

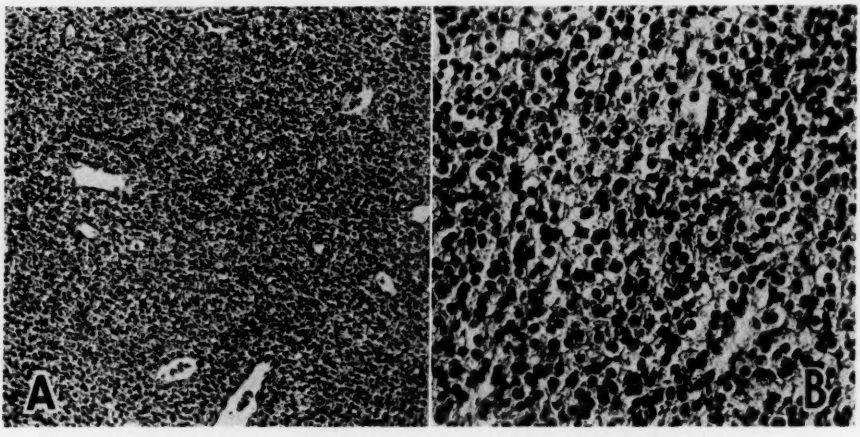


Fig. 3.—*A*, low power view of parathyroid tissue removed at operation. Cells are of chief cell type and show typical picture of hyperplasia; × 100. *B*, higher magnification of same tissue; × 450.

Microscopically (fig. 3) the entire mass appeared to consist of parathyroid tissue, and a diagnosis of hyperplasia of the parathyroid gland was made.

Three days after operation, the patient complained of tingling sensations in the extremities and Chvostek's sign was present. The serum calcium was 4.3 mg. and the phosphorus 8.4 mg. per 100 ml. The hypocalcemic symptoms were relieved by intravenous administration of calcium gluconate.

A retrograde pyelogram showed bilateral hydronephrosis and megaloureter. The ureterovesical junction was dilated instrumentally because it was thought that obstruction might be present. Two months after his admission a transurethral resection of the prostate was performed. Little tissue was actually removed. The microscopic diagnosis was fibrosis and chronic urethritis.

Four months after his admission it was noted that the patient's general condition and mental outlook had improved considerably, although the nonprotein nitrogen level remained elevated. The calcified plaques in the hands and legs and the masses over the scapulas (figs. 1*B* and 2*B*) had grown much smaller. At this time a portion of a subcutaneous plaque and a wedge of bone from the iliac crest were removed for microscopic study. The plaque (fig. 4) showed areas of calcium salt deposition with a granulomatous reaction in the subcutis. The iliac bone biopsy (fig. 5) exhibited changes consistent with healing osteitis fibrosa cystica. After six months in the hospital, the patient was discharged.

He reentered six weeks later because of repeated emeses, shooting pains in the distal portions of the upper extremities and increased fatigability. The pigmentation of the skin had increased. The plaques containing calcareous material had greatly regressed and were no longer palpable.

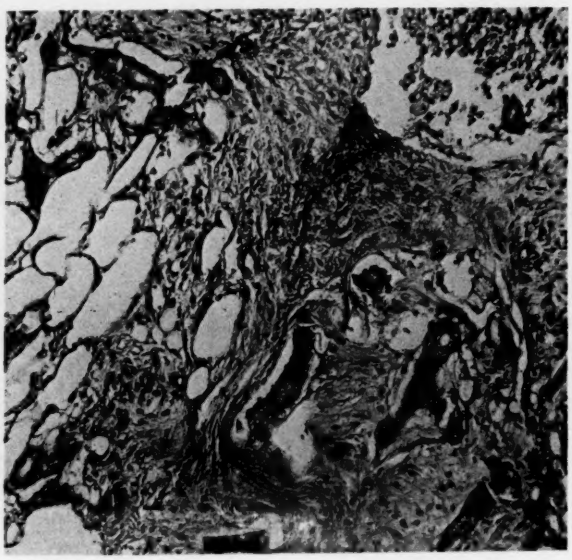

Fig. 4.—Subcutaneous plaque. Irregular darkly staining areas represent calcium. They are surrounded by fibrous tissue in which giant cells, plasma cells and lymphocytes are present; × 100.

Laboratory studies on this second admission showed the following results: The urine had a 3+ reaction for albumin, with many pus cells. The hemoglobin concentration was 10 Gm. per 100 ml. There were 2,950,000 red blood cells and 7,900 white blood cells per cubic millimeter, with 88 per cent neutrophils, 11 per cent lymphocytes and 1 per cent monocytes. Nonprotein nitrogen was 166 mg., urea nitrogen 150 mg., uric acid 5.6 mg., creatinine 20 mg., serum calcium 4.7 mg. and inorganic phosphorus 16.2 mg., per 100 ml. Alkaline phosphatase measured 12.9 Bodansky units; total serum proteins were 8.5 Gm. per 100 ml., with 6.0 Gm. of albumin and 2.5 Gm. of globulin.

Five days after his readmission an acetone odor to the breath was noted. The patient became mentally disoriented, nervous, excited and somewhat delirious. He lapsed into coma and died six days later (six months after the first admission and approximately 1½ years after the onset of the disabling symptoms).

*Gross Autopsy Observations.*—The body of a well developed and well nourished white man, weighing 63 Kg. and measuring 163 cm. in length, was seen 45 minutes after death. A diffuse bronze coloration of the skin was noted. The peritoneal, pleural and pericardial cavities were normal.

The heart was of normal size, weighing 360 Gm., and the only structural abnormality was calcification of the walls of the large coronary arteries without any attendant decrease in their lumens. The aorta was grossly normal, but the medium-

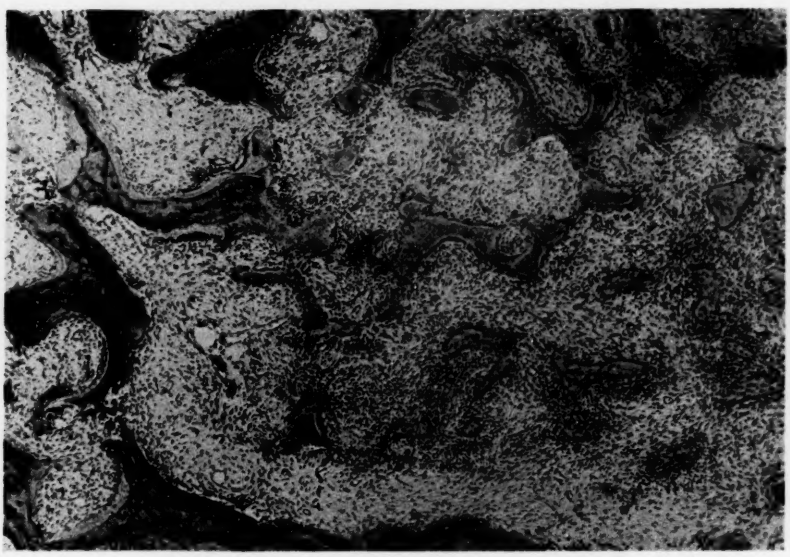

Fig. 5.—Iliac bone. Typical lesion of osteitis fibrosa with evidences of healing. There are narrow, faintly staining and newly formed trabeculae composed mostly of the osteoid which is laid down preparatory to calcium salt impregnation. Rows of plump osteoblasts are alined along the margins. At the periphery some of the mature bone spicules are undergoing resorption. A number of osteoclasts is seen in the lower left corner of photomicrograph; × 100.

sized arteries throughout the body, such as the iliac, hypogastric, mesenteric and celiac arteries, showed profuse calcification of their walls such as to give them a brittle eggshell feel when palpated and compressed. No luminal obstruction was noted.

The lungs exhibited dependent edema and congestion, with mild bullous emphysema of the upper lobes and no gross evidence of consolidation. A Ghon nodule was not seen, but a group of lymph nodes at the right hilus was enlarged and revealed, on section, foci of gray-white caseous material.

The ureters were conspicuously dilated and tortuous throughout and measured 1.5 to 2 cm. in diameter. They were dissected from the pelvis to the bladder, and no obstruction was found, although a number of incomplete valvelike mucosal redundancies were projecting into the lumen. The wall of the ureter was slightly thickened. The kidneys were flabby and had prominently dilated pelves. The left kidney weighed 120 Gm. and the right 80 Gm. after the dilated pelves had been opened and cloudy white urine allowed to escape. The capsules of the kidneys were removed with difficulty, revealing a coarsely granular surface with many small and

Fig. 6.—Artery. Profuse medial calcification is clearly evident. The dark bands, frequently fragmented, represent calcium deposits; × 32.

large depressed scars and alternating elevated pale parenchyma. On section distention of the calyxes and pelves, more pronounced on the right, was seen with only shells of corticomedullary tissue remaining. The cortices were thus greatly reduced in thickness and were pale with granular yellow streaks running perpendicular to the surface.

The urinary bladder contained 500 ml. of cloudy urine. Its mucosa was pale but not trabeculated. Little prostatic tissue was seen, and no evidence of obstruction at the vesical neck or in the prostatic urethra was present.

Four tan-gray nodules of parathyroid tissue were found after careful search in the capsule of the thyroid and in the areolar tissue between the thyroid and the vascular sheaths. These included an irregular mass of parathyroid tissue amid an area of fibrosis at the left lower pole of the thyroid where the parathyroid tumor had been previously removed. The diameter of these nodules ranged between 0.5 and 0.8 cm.

Malunion of a fracture involving the midportion of the femoral neck on the right, with fibrous tissue uniting the fragments, was seen. A few ribs showed moderate enlargement at the costochondral junction. No other osseous changes were observed.

No trace could be found at necropsy of the calcified soft tissue masses noted during life.

The spleen, pancreas, liver, gallbladder, gastrointestinal tract, adrenal glands, testes and thyroid were all grossly normal.

The brain was not examined.

*Microscopic Descriptions.*—Heart and Blood Vessels: The heart was microscopically normal except for medial calcification of portions of the coronary arteries. The aorta also showed slight intimal thickening and early atheroma formation. Sections of several medium-sized arteries all displayed an advanced degree of medial calcification (fig. 6).

Lungs: The bronchi and bronchioles contained dense polymorphonuclear exudate, with extension of the inflammatory process to neighboring alveoli. The lung parenchyma was otherwise normal. Lymph nodes from the right hilus were enlarged and contained nodules showing peripheral fibrosis and central caseation.

Kidneys: The renal tissue was decidedly contracted. In many areas the entire cortex and medulla were seen within one low power microscopic field. The glomeruli were decreased in number, with complete fibrosis and obliteration of many, while numerous others showed capsular thickening and a few exhibited adhesions between the tuft and the capsule. Extensive atrophy of the convoluted tubules had taken place with interstitial replacement fibrosis and intervening areas showing a compensatory dilatation of the functioning tubules. Many of the latter contained eosin-staining hyaline casts. Reactive epithelial proliferation and lymphocytic infiltration were occasionally noted about these casts. In conjunction with the tubular atrophy there were scattered foci of calcium salt deposition within these tubules, and even in the fibrous interstitial tissues (fig. 7). A dense but patchy lymphocytic cell infiltration was noted throughout the cortex and medulla, extending to just beneath the transitional epithelium of the pelvis. In the medulla the fibrosis and atrophy were even more pronounced than in the cortex. Hyaline casts with and without cellular reaction were present in the collecting tubules. The renal arteries had thick walls, with fibrosis of their media.

Ureters: The wall was slightly thickened. An atrophic transitional cell epithelium was present with diffuse chronic inflammatory cell infiltration in the lamina propria.

Urinary Bladder: The histologic picture was the same as that of the ureters.

Testes: Little evidence of spermatogenesis was present. Interstitial fibrosis and atrophy of the seminiferous tubules were noted.

Parathyroids: Microscopic sections of nodules of parathyroid tissue, varying in size from minute to about 2½ times normal, were examined. A thin capsule was present about each gland. The parenchyma consisted of large sheets of chief cells of normal size which had a typically clear or vacuolated cytoplasm with well defined cell outlines. The nuclei were vesicular, lacked nucleoli and did not show mitotic figures. A few oxyphil cells in rare small aggregations were present. The

monotony of the cellular pattern was broken only by numerous thin-walled vascular channels. Fat cells were absent in all except one gland, and here only a few were present.

In one minute nodule within the capsule of the thyroid the cells were of the *Wasserhelle* type and formed small acinar structures with basally situated nuclei and abundant clear cytoplasm. A section of parathyroid tissue remaining at the

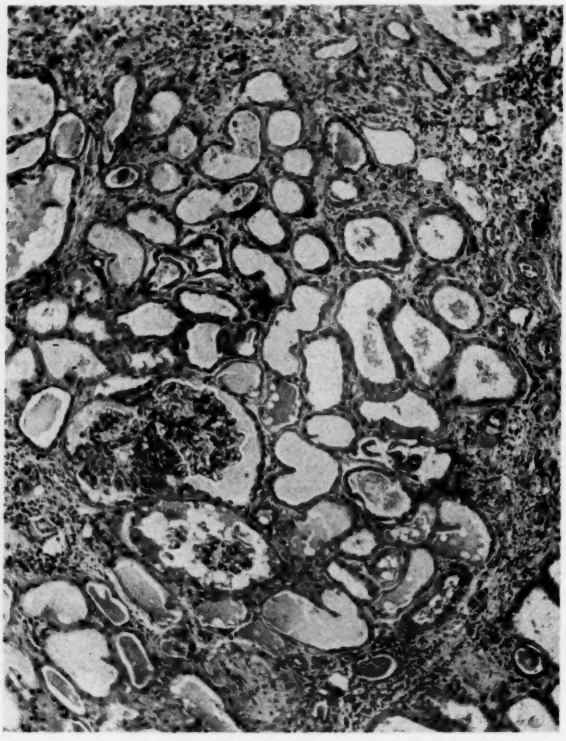

Fig. 7.—Kidney. In this section is a single intact glomerulus with dilatation of the surrounding tubules. A completely fibrotic glomerulus is also seen. Many hyaline casts are present within the tubules. Black areas adjacent to some of the tubules represent calcifications. Increase in stromal fibrous tissue with lymphocytic cell infiltration is obvious; × 100.

site of previous operation showed a granulomatous reaction about suture material. Ingrowing strands of fibrous tissue were separating small lobules of parathyroid chief cells.

Bone: Sections from the vertebrae, ribs, sternum and femur showed an essentially similar picture (fig. 8). There were islands of hematopoiesis, but the major

portion of the marrow space was occupied by large numbers of small irregular trabeculae of coarse fibrillar bone lying in a fibrous matrix. The spongiosa showed predominant osteoblastic new bone formation with rows of plump osteoblasts alined along the trabeculae, and the spicules had moderately wide osteoid margins. There was no apparent delay in calcium salt deposition on the osteoid material.

Fig. 8.—Vertebral bone. This specimen of bone removed at autopsy shows a completely different picture than that seen in figure 5. Now the bony trabeculae are broad, numerous and mature. Only an occasional osteoclast is seen. Osteoblasts are less active and less prominent. Fibrous marrow is unchanged; × 100.

Osteoclastic activity was also seen, with multinucleated osteoclasts lying in lacunar spaces carved out of the bone. However, this lytic process was greatly exceeded by the deposition of new bone. The cortices were thin throughout, with enlarged lacunar spaces containing fibrous tissue. Here, too, new bone was being laid down. The fibrous tissue was vascular and moderately dense, and there was no evidence of

inflammatory reaction. Several small cysts were seen in the femur. These areas were surrounded by myeloid and erythroid cells.

At the enlarged costochondral junctions, the line of endochondral ossification was widened and irregular and the columns of cartilage cells were distorted (fig. 9). There was active osteoblastic activity, with new bone matrix being laid down both on calcified cartilage remnants and onto already formed bone spicules. Osteoclastic

Fig. 9.—Rib. Extent of bony "repair" with filling in of the porotic areas by many new trabeculae can be seen in this low power view. At chondral end of the rib are irregularities of the cartilage with moderate expansion of end of bone. These irregularities are consistent with the changes seen in "renal rickets"; × 10.

activity in this region was also notable. Irregular tongues of vascular elements were extending into the cartilage from the marrow spaces. The costochondral junction of other ribs showed a wavy but not irregular cartilage line.

Sections from the site of fracture in the femur revealed a predominantly fibrous tissue uniting the fragments.

The spleen, pancreas, liver, adrenal glands, seminal vesicles, prostate and thyroid displayed no histologic changes of note.

*Anatomic Diagnoses.*—The anatomic diagnoses were: hydroureter and hydronephrosis with chronic pyelonephritis, ureteritis and cystitis; hyperplasia of parathyroid glands, predominant in one gland; healing generalized osteitis fibrosa cystica; fibrous union of pathologic fracture of neck of right femur; metastatic calcification of soft tissues (surgical specimens) and of medium-sized arteries; coronary artery sclerosis; acute bronchopneumonia and tuberculosis of right hilar lymph nodes.

*Summary.*—This 27 year old man had a history of renal disease since childhood. He presented the clinical picture of renal insufficiency, metastatic calcifications, osteoporosis, pigmentation of the skin and a palpable mass in the region of the lower pole of the thyroid on the left. Except for the palpable mass, the clinical features were those of renal osteitis fibrosa generalisata, and for this reason a biopsy of the mass was taken. The histologic diagnosis on examination of this tissue was hyperplasia of the parathyroid, and the syndrome was thus complete. In this case there was the added feature of the deep reddish brown pigmentation of the skin. This will be discussed later.

It is of interest that, following removal of the mass of hyperplastic parathyroid tissue, steady regression of the subcutaneous calcifications and healing of the bone lesions began despite an unchanged renal status. Study of the laboratory findings before and after operation (table 2) shows the striking drop in serum calcium and the decided rise in alkaline phosphatase. This rise correlates well with the evidences of new bone formation observed on biopsy and later at autopsy. The fall in the serum calcium was associated with severe tetany postoperatively.

A retrograde pyelogram showed the presence of megaloureter and hydronephrosis. This was confirmed at autopsy.

The therapy included symptomatic measures, a high calcium and low phosphorus diet and the administration of aluminum hydroxide. Calcium salts were given parenterally when the tetanic manifestations developed. There was little change in the general status of the patient, although resorption of the subcutaneous calcium deposits occurred and evidences of bone healing appeared. He died in uremia after six months of observation.

The autopsy observations confirmed the presence of renal disease. Hyperplasia of the remaining parathyroids and the healing lesions of osteitis fibrosa were observed. The subcutaneous calcifications had completely disappeared at this time.

## COMMENT

*Renal Disease.*—In the cases of renal osteodystrophy with or without metastatic calcifications, a variety of renal lesions has been described.[8] In about one half of the cases a congenital renal disorder was present,

while the remainder were due to various acquired lesions. The congenital diseases included hypoplastic kidney, polycystic kidney and renal insufficiency resulting from the congenital presence of urethral valves or ureterovesical dysfunction. The acquired renal diseases included interstitial nephritis of children, subacute and chronic glomerulonephritis, pyelonephritis and arteriosclerotic atrophy of the kidneys. The outstanding factor linking these diverse renal changes has been the long duration of the disease. More specifically, the long-standing renal insufficiency caused serious metabolic disturbance, changes in the serum calcium and phosphorus levels and chronic acidosis. After the alterations in body chemistry, parathyroid hyperplasia and skeletal changes manifested as diffuse osteitis fibrosa took place. Older persons apparently cannot tolerate a preuremic or uremic state as well as can children. In the usual renal disease in adults death ensues before parathyroid or skeletal changes can occur to any great degree, although lesser degrees of parathyroid hyperplasia and osteitis fibrosis are not uncommonly seen at necropsy. It is for this reason that advanced renal osteodystrophy is so much less common in adults than in children and progression of the disease to the stage of metastatic calcifications is most unusual.

The pathogenesis of the tissue changes following chronic renal dysfunction is not completely settled. Mitchell [5] postulated that in severe renal insufficiency a shift in phosphorus excretion from the kidney to the bowel takes place. With this intestinal excretion of the phosphates there is combination with the dietary calcium, forming insoluble calcium phosphate, which results in a decrease in available calcium for absorption from the bowel. Albright, Drake and Sulkowitch [9] supported this theory and also showed that an increased serum phosphate, such as occurs in renal insufficiency, stimulates parathyroid activity.[13] Further confirmation is found in the metabolic studies of Liu and Chu,[14] who demonstrated that in renal osteodystrophy calcium was lost in the stool in addition to a large amount of phosphates.

The skeletal lesions have been thought in the past to be due to direct action of the parathyroid hormone on the bone by Thomson and Collip [15] and Park and Elliot.[4] More recently, Collip [16] changed his position and expressed the opinion that the evidence is against a direct

13. Drake, T. G.; Albright, F., and Castleman, B.: Parathyroid Hyperplasia in Rabbits Produced by Parenteral Phosphate Administration, J. Clin. Investigation **16**:203, 1937.

14. Liu, S. H., and Chu, H. I.: Studies of Calcium and Phosphorus Metabolism with Special Reference to Pathogenesis and Effects of Dihydrotachysterol (A. T. 10) and Iron, Medicine **22**:103, 1943.

15. Thomson, D. L., and Collip, J. B.: The Parathyroid Glands, Physiol. Rev. **12**:309, 1932.

16. Neufeld, A. H., and Collip, J. B.: The Primary Action of the Parathyroid Hormone, Endocrinology **30**:135, 1942.

effect of parathyroid hormone on bone. Jaffe, Bodansky and Chandler [17] were able to produce osteitis fibrosa in dogs by a low calcium diet and parenteral administration of ammonium chloride to produce acidosis. They concluded that acidosis alone was sufficient to account for the skeletal changes. While acidosis does exert an effect on calcium and phosphorus metabolism, it is probably only a contributing factor in producing the skeletal lesions by potentiating the reduced dietary intake of calcium to promote withdrawal from the bone. Chown [18] was of the opinion that a pituitary factor is important in the production of renal rickets. This theory has not been widely accepted. Pope and Aub [19] stated that no consistent or conclusive evidence of pituitary-parathyroid relationship has been advanced.

*Parathyroid Glands.*—Since Bergstrand [6] first noted the association of parathyroid hyperplasia and long-standing renal disease, it has become evident that such hyperplasia is a constant observation in chronic renal insufficiency. This is true in children with the syndrome of renal rickets, as well as in adults not showing the severe bone changes seen in members of the younger age groups. In the earliest reported cases of renal osteodystrophy, parathyroid enlargement was not found because it was not sought. Since realization of the interrelationships of kidney, bone and parathyroid, however, hyperplasia has been constantly found when looked for. Gilmour and Martin [20] made a statistical analysis of the weights of parathyroid glands in nephritis and other renal disorders and reported higher mean weights in these diseases than in other disease groups. Pappenheimer and Wilens [21] observed the increase in the weight of the parathyroids to be roughly proportional to the severity and extent of the renal disease and to the degree of renal insufficiency.

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17. Jaffe, H. L.; Bodansky, A., and Chandler, J. P.: Ammonium Chloride Decalcification, as Modified by Calcium Intake: The Relation Between Generalized Osteoporosis and Ostitis Fibrosa, J. Exper. Med. **56**:823, 1932.

18. Chown, B., and Lee, M.: Renal Rickets and Dwarfism as a Pituitary Disease, Am. J. Dis. Child. **53**:117 (Jan., pt. 1) 1937.

19. Pope, A., and Aub, J. C.: The Parathyroid Glands and Parathormone, New England J. Med. **230**:698, 1944.

20. Gilmour, J. R., and Martin, W. J.: The Weight of the Parathyroid Glands, J. Path. & Bact. **44**:431, 1937.

21. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of the Parathyroid Glands in Renal Disease, Am. J. Path. **11**:73, 1935. Pappenheimer, A. M.: Effect of Experimental Reduction of Kidney Substance upon Parathyroid Glands and Skeletal Tissue, J. Exper. Med. **64**:965, 1936.

Castleman and Mallory [22] did much to clarify the pathologic changes in the parathyroids by careful histologic studies in a large series of cases. They reported that there were three main types of parathyroid diseases: (1) adenoma, (2) primary hyperplasia (water-clear cell type) and (3) secondary hyperplasia (chief cell type), and that these could be differentiated usually on the basis of the gross and microscopic observations.

The adenoma is characterized by localized proliferations of any of the cell types observed in the parathyroids: chief cell, oxyphil cell and water-clear cell. One gland, or at the most two, is involved, and the remaining parathyroid tissue is histologically normal. The adenomas vary considerably in size, from those evident only under the microscope to ones measuring many centimeters and weighing up to 120 Gm.[23] The adenomas most frequently involve only part of the gland, leaving a rim of compressed normal parathyroid tissue. The microscopic appearances were well described by Castleman and Mallory.[10d]

Primary hyperplasia is due to a diffuse increase in the size and/or number of water-clear cells, giving rise to parathyroid enlargement and symptoms of primary hyperparathyroidism. In this type there is enlargement due to an unknown stimulus,[24] and the kidneys are not primarily affected. All four parathyroid glands are enlarged and show a similar histologic picture.

Hyperplasia of the parathyroids secondary to renal insufficiency affects all the glands and usually to an almost equal degree. Predominant enlargement of one gland, as noted in the present case, is exceptionally rare, although variations in size have been reported. There is a characteristic microscopic appearance in hyperplasia, with the chief or principal cells showing great increase in number. The cells are not enlarged and are not unlike normal chief cells. They are usually arranged in broad sheets that lie in a delicate reticular and highly vascular stroma in which small clumps or groups of oxyphil and small water-clear cells may also be present. Only occasionally are acinar arrangements seen. Mitotic figures are not found, and the capsule is always intact. Normal parathyroid tissue and the usual fat cells are not present, the entire gland participating in the hyperplasia to an equal degree.

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22. (*a*) Castleman and Mallory.[10d] (*b*) Castleman, B., and Mallory, T. B.: Parathyroid Hyperplasia in Chronic Renal Insufficiency, Am. J. Path. **13**:553, 1937.

23. Sharpe, H. S.: Hyperparathyroidism Associated with Osteitis Fibrosa, Canad. M. A. J. **40**:164, 1939.

24. Albright, F.; Sulkowitch, H. W., and Bloomberg, E.: Hyperparathyroidism Due to Idiopathic Hypertrophy (Hyperplasia?) of Parathyroid Tissue: Follow-Up Report of 6 Cases, Arch. Int. Med. **62**:199 (Aug.) 1938.

Because of this known diffuse parathyroid enlargement in renal insufficiency, it has been the policy of authors automatically to exclude from consideration as hyperplasia cases in which only one parathyroid gland was increased in size and weight. In the first case of Gilmour and Martin,[20] great enlargement and hyperplasia of only one gland were present, with other glands normal, in a patient with early nephritis. Anderson [8] stated that it would be more logical to consider this case as one of adenoma rather than as one of hyperplasia. However, in some of the other cases of this syndrome in which the size or weight of the parathyroids was given, one of the glands was two or three times larger than the others.[25] In our case there was predominant hyperplasia of one gland, so much so that it was easily palpable on physical examination. At autopsy six months later a number of other parathyroid glands were also observed, and, although not greatly enlarged, microscopically all showed typical hyperplasia identical with that seen in the large gland. This observation is important because it shows that single enlarged parathyroid glands are not necessarily adenomas, but that predominant increase in size may occur in one of the affected glands. In other instances, such as the cases cited above, transition in the size of hyperplastic glands was such that the great hyperplasia reported in our case is not unique, but rather an exaggeration of a finding noted before. The important feature in our case is that a palpable parathyroid mass in the neck need not be an adenoma.

The possibility that we are dealing here with a true adenoma of the parathyroid must be considered because of the size of the gland and because of the remarkable alteration in the clinical course of the patient following its removal. If this had been an adenoma, it was a result of stimulation by physiologic changes or a pure coincidence. Neoplasms are not known to develop in the body as a result of physiologic stresses, and the occurrence of a completely fortuitous neoplasm of the parathyroid gland in this case would indeed be remarkable. The histologic picture is that of hyperplasia of the parathyroid tissue rather than that of adenoma, and the clinical features of long-standing renal insufficiency are those associated with parathyroid hyperplasia. These facts, in conjunction with the demonstrated variability in size of hyperplastic parathyroid glands, lead us to conclude that we are dealing here with hyperplasia rather than neoplasia. The histologic diagnosis on this parathyroid gland has been confirmed by Mallory.[26]

*Changes in the Skeleton.*—The skeletal changes in hyperparathyroidism are essentially identical, whether caused by primary or secondary

25. (*a*) Herbert and others.[11] (*b*) Magnus, H. A., and Scott, R. B.: Chronic Renal Destruction and Parathyroid Hyperplasia, J. Path. & Bact. **42**:665, 1936.

26. Mallory, T. B.: Personal communication to the authors.

parathyroid overactivity. The lesions [27] consist of extensive decalcification (osteoporosis) of all the bones, with pronounced osteoclastic activity and usually a diffuse marrow fibrosis. Despite the widespread use of the term "osteitis," there is no evidence of any inflammatory process. In the primary hyperparathyroid lesions, whether caused by adenoma or primary hyperplasia, bone cysts are common and diffuse resorption of bone more marked. In secondary hyperparathyroidism the lesions tend to be somewhat more diffuse and less severe. However, cystic areas do occur, and lesions indistinguishable clinically or histologically from the primary form of disease may be produced.

The pathologic changes affect both the cortical and the cancellous bone and also the marrow spaces. In the less advanced lesion a microscopic picture known as "dissecting resorption of bone" is produced in which the bony trabeculae have scalloped margins in which osteoclasts lie and give the appearance of having eroded the bone in these areas. Frequently, the osteoclastic lacunas are quite deep and there is an associated fibrosis of the adjacent tissue. This may be seen even though the remainder of the marrow spaces is filled with their normal content of hematopoietic cells and adipose tissue. In severer lesions there may be complete fibrosis of the marrow spaces, with increased vascularity, areas of hemorrhage and hemosiderin accumulation. The trabeculae are thin and fewer. There are numerous osteoclasts closely applied to the remaining bone, and in areas where the spongiosa has completely disappeared there may be accumulations of the osteoclastic giant cells, giving the appearance of a giant cell tumor. Evidence of new bone deposition is minimal, unless the stimulus toward osteoporosis has been removed and healing is taking place. The cortical bone is similarly affected and may become very thin.

The bony changes in secondary hyperparathyroidism at the epiphysial line depend on the rate of endochondral bone formation; thus, the most extensive lesions are seen in children. There is proliferation of the cartilage to form large masses, with deficient production of new bone. The roentgen picture produced by this lesion is similar to that of true rickets and has been responsible for the widespread usage of the term "renal rickets." In fact, even the microscopic picture may resemble that of long-standing rickets of the low phosphorus type [4] but can be differentiated by the absence of wide osteoid borders on the metaphysial side of the growth plate, unless true rickets is coexistent. In adult renal osteitis fibrosa the condition is easily differentiated from osteomalacia by the same feature.

In the present case the osseous lesions were predominantly those of healing. There was a decided difference between the changes observed

27. Park and Elliott.[4] Jaffe, H. L.: Hyperparathyroidism, Bull. New York Acad. Med. **16**:291, 1940.

in the portion of iliac bone removed during life and those seen in the bones examined at time of autopsy. In the later specimens pronounced deposition of new bone and greatly decreased osteoclastic activity were evident. In some areas, the bone had even become dense. Because of this, it would have been difficult to diagnose the bone lesions if the biopsy specimen had not been available. Study of the available material makes it clear that undoubted osteitis fibrosa had been present and that definite "healing" of the bone lesions was in process at the time of death.

*Metastatic Calcification.*—Since the first reported cases of Virchow,[28] it has been known that metastatic calcification is seen in the presence of severe renal damage. Barr emphasized this in his review of the subject[29] and stated that it was difficult to find a case in which renal involvement could be eliminated as a factor. More recently, Mulligan[30] reviewed the reported cases of metastatic calcification. Such calcification is often seen as a feature of destructive bone lesions and has been noted in multiple myeloma,[31] Paget's disease (osteitis deformans),[32] leukemia,[33] carcinoma which has metastasized to bone[34] and hyperparathyroidism due to adenoma.[35] It was also described in cases of hypervitaminosis D[36] and has been reported as due to a basophil adenoma of the pituitary.[12] The occurrence of calcium deposits in the soft tissues in renal osteitis fibrosa was first mentioned as an integral feature of the syndrome by Albright and his associates.[9] Now it appears that renal insufficiency with secondary hyperparathyroidism and subsequent skeletal lesions is one of the commonest causes of metastatic calcifications. While Barr stated that the calcific lesions are located chiefly in the kidneys, heart, gastric mucosa and lungs, it appears from the reported cases of this syndrome that they have been more frequently encountered in the arteries and subcutaneous and periarticular tissues. The reason

28. Virchow, cited by Barr, D. P.: Physiol. Rev. **12**:593, 1932.

29. Barr, D. P.: Pathological Calcification, Physiol. Rev. **12**:593, 1932.

30. Mulligan, R. M.: Metastatic Calcification, Arch. Path. **43**:177 (Feb.) 1947.

31. Barr, D. P., and Bulger, H. A.: The Clinical Syndrome of Hyperparathyroidism, Am. J. M. Sc. **179**:449, 1930.

32. Wells, H. G., and Holley, S. W.: Metastatic Calcification in Osteitis Deformans (Paget's Disease of Bone), Arch. Path. **34**:435 (Aug.) 1942.

33. Grayzel, D. M., and Lederer, M.: Metastatic Calcification: Report of 2 Cases, Arch. Int. Med. **64**:136 (July) 1939.

34. Egoville, J. W.: Metastatic Calcification in a Case of Carcinoma of the Breast, Arch. Path. **26**:1047 (Nov.) 1938.

35. Heuper, W.: Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, Arch. Path. **3**:14 (Jan.) 1927.

36. Bauer, J. M., and Freyberg, R. H.: Vitamin D Intoxication with Metastatic Calcification, J. A. M. A. **130**:1208 (April 27) 1946. Mulligan, R. M.: Metastatic Calcification Associated with Hypervitaminosis D and Haliphagia, Am. J. Path. **22**:1293, 1946.

for this localization is not evident, although many factors, such as local increase in $p_H$ of the tissue, the serum concentration of calcium and of phosphates, phosphatase activity and local changes in the tissues, have been mentioned.

Herbert, Miller and Richardson [11] collected the reported cases of metastatic calcification in renal osteodystrophy and discussed the mechanism by which extraskeletal calcium deposits occur. They were of the opinion that the alteration of the calcium and phosphate equilibrium in the blood due to renal disease is the important physiologic change. With the retention of phosphates in renal insufficiency there is ordinarily a concomitant decrease in the serum calcium level. Stimulation of the parathyroid glands by the increased phosphate level (or decreased calcium level) leads to withdrawal of calcium from the bones; thus, there is elevation of the serum calcium to near normal or slightly above normal levels. With the renal dysfunction preventing adequate phosphate excretion, there may be oversaturation of the blood by the calcium and phosphate ions which promotes the deposition of calcium phosphate into tissues where conditions are favorable. Herbert and his associates emphasized that it is necessary for the calcium to be at near normal or normal levels, as well as for the phosphate level to be increased, before calcium deposits could occur in the soft tissue. Bass and Pakter [37] followed a case in which soft tissue calcifications occurred while the patient was under their observation. Calcium and phosphate determinations before and after the tissue change showed that an increase in the serum calcium level took place just before the time of soft tissue calcification.

In our case, the metastatic calcifications were present when the patient was first seen and the calcium and phosphate levels were within the range predicted by Herbert and his colleagues. As seen from table 2, the inorganic phosphates were elevated and the calcium level was within normal limits. It can also be seen that immediately after removal of a substantial mass of hyperplastic parathyroid tissue the calcium level decreased precipitously to tetanic levels. With this decrease in serum calcium there was a steady resorption of soft tissue calcium deposits over several months. This calcium was apparently deposited in the bones because the alkaline phosphatase, a measure of osteoblastic activity, became elevated at this time.

This complete disappearance of metastatic calcium deposits in the soft tissue is a phenomenon which has not been previously noted in these cases. While repair of the bone lesions following resection of a parathyroid adenoma is known to occur, because the stimulus to decal-

37. Bass, M. H., and Pakter, J.: Congenital Polycystic Kidneys with Secondary Bone Changes (Renal Hyperparathyroidism: Renal Rickets), J. Mt. Sinai Hosp. **4**:882, 1938.

cification has been removed, dissolution of the calcium deposits in this instance is remarkable because the factors acting to cause parathyroid hyperplasia had not changed. It seems inconsistent and paradoxic that the remaining parathyroid tissue had not become more hyperplastic and thus acted to maintain the status quo and prevent mobilization of the calcium deposits. This is best explained by us by the hypothesis that the hyperplasia of the parathyroids had exceeded the optimum and that as a result of the stimulus to increased activity excess parathyroid function had occurred. It is also noteworthy that healing and recalcification of the skeletal tissue took place, probably as an effect of utilization of the calcium mobilized from the soft tissue deposits. Despite the conspicuous changes in extraskeletal calcifications and the alterations in the calcium and phosphorus levels so that the body metabolism was much more in equilibrium, there was no variation in the clinical course because of the irreversible severe renal disease.

*Pigmentation.*—The pigmentation of the skin noted in this case was quite striking and drew attention, clinically, to the possibility of involvement of the adrenal glands. After the presence of severe renal impairment was established, it was decided that the pigmentation was on the basis of long-standing renal disease. At autopsy normal adrenal tissue was observed, lending confirmation to the latter clinical impression. Dermal pigmentation in chronic renal insufficiency has been long known, but little has been written about it. In reviewing the literature on childhood renal osteodystrophy, relatively few cases were found in which the presence of abnormal pigmentation of the skin was noted.[38] In some of those cases a yellowish coloration was present, while in others a brown or bronze pigmentation was described. However, in the reported cases of this syndrome, pigmentation of the skin was described in 53 per cent. In none of the cases reported did the skin discoloration excite comment, although it must have been considered abnormal. The presence of skin pigmentation may well be included as one of the features of this syndrome because it is present in a significant percentage of the cases. Unfortunately, the skin of our patient was not examined closely; the one section available for study was taken from an area of subcutaneous calcification and did not show any increased pigmentation.

The cause of the increased skin coloration is not known. Unger[39] stated that urochrome pigments may accumulate in the tissues because of failure of excretion through the kidneys. Becher[40] was of the view

38. Ellis, A., and Evans, H.: Renal Dwarfism: A Report of 20 Cases with Special Reference to Its Association with Certain Dilatations of the Urinary Tract, Quart. J. Med. **26**:231, 1933.

39. Unger, H.: Report on Skin Pigmentation in Renal Insufficiency, München. med. Wchnschr. **78**:707, 1931.

40. Becher, E.: Investigations of Occurrence of Yellow Skin Pigmentation, München. med. Wchnschr. **77**:1922, 1930.

that the yellowish skin pigment is related to the indole acetic acid pigments which are normally excreted in the urine. These pigments are colorless until exposed to light. Becher postulates that such pigment accumulating in the skin because of failure of renal elimination is then changed to a colored compound. A relationship between pigmentation of the skin and polycystic kidney is reported in two cases by Formijne and French.[41] They hypothesized that the pigment is melanin which had accumulated owing to failure of the renal excretory function. No conclusions are possible at present because of inadequate evidence, but certainly this is a subject which deserves further study.

*Therapy.*—Because of the presence of long-standing irreversible renal damage, there is actually little that can be done therapeutically toward cure of the disease. However, it is an encouraging fact that many children and even older persons with this syndrome can withstand a uremic state for exceptionally long periods. This is probably related to the gradual decrease in renal function and to the frequent lack of an inflammatory component in the renal disease. Because the patient may live for a long time despite his altered body chemistry, attempts at improving chemical and skeletal abnormalities are possible. A high calcium, low phosphorus diet is recommended [42] in order to increase the exogenous supply of calcium and to decrease the demands on the bone depots. To further the absorption of calcium, drugs, such as aluminum hydroxide [43] and ferric ammonium chloride,[14] have been administered in the belief that they will combine with the phosphates excreted into the intestine and thus permit absorption of calcium. Therapy with dihydrotachysterol (AT-10) also has been shown by Liu and Chu [14] to promote the absorption of calcium in the presence of renal insufficiency. Administration of vitamin D was of no benefit in their cases.

In view of the acidotic state of the patient, administration of alkalis may be beneficial. Albright [44] recommended use of sodium bicarbonate or a mixture of sodium citrate and citric acid. In line with this, Graham

41. Formijne, P., and French, E. B.: Two Cases of Pigmentation of the Skin in Polycystic Degeneration of the Kidney, Guy's Hosp. Rep. **88**:129, 1938.

42. Shelling, D. H., and Remsen, D.: Renal Rickets: Report of a Case Showing 4 Enlarged Parathyroids and Evidence of Parathyroid Hypersecretion, Bull. Johns Hopkins Hosp. **57**:158, 1935.

43. Helfet, A. J.: A New Conception of Parathyroid Function and Its Clinical Application: A Preliminary Report on the Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminum Acetate, Brit. J. Surg. **27**:651, 1940.

44. Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in a Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7, 1940.

and Oakley [45] reported that correction of the acidosis improves renal function. Albright [46] emphasized that renal insufficiency in the presence of hyperparathyroidism is an indication that less parathyroid tissue should be removed surgically; otherwise intractable tetany might result. This advice is particularly important in cases of adenoma or primary hyperplasia of the parathyroids in which the proper therapy is surgical. A similar situation existed in our case in that removal of the parathyroid mass, despite the presence of other hyperplastic gland tissue, resulted in severe tetany and considerable lowering of the serum calcium level.

## SUMMARY AND CONCLUSIONS

A case is presented, with the autopsy observations, which corresponds closely to the syndrome of chronic renal disease, decalcification of bone, parathyroid hyperplasia and metastatic calcification as first described by Albright and his associates. This is the eighteenth such case reported in the literature.

The unique feature in this case of predominant enlargement of one parathyroid gland simulating an adenoma is discussed.

It is pointed out that pigmentation of the skin, such as was present in this case, occurs in more than 50 per cent of the reported cases of the syndrome. Because of the frequency of this observation, it is suggested that skin pigmentation properly deserves consideration as an integral component of the syndrome. The cause of pigmentation of the skin in renal insufficiency warrants further study.

The clinical and pathologic findings in the syndrome are reviewed, and the pathogenesis is discussed.

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45. Graham, O., and Oakley, W. G.: The Treatment of Renal Rickets, Arch. Dis. Childhood **13**:1, 1938.

46. Albright, F.: The Parathyroids—Physiology and Therapeutics, J. A. M. A. **117**:527 (Aug. 16) 1941.

# USE OF CORTISONE AND ADRENOCORTICOTROPIC HORMONE IN ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

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WE HAVE investigated the influence of cortisone and of pituitary adrenocorticotropic hormone (ACTH) on 34 patients with a variety of illnesses. Of this group 14 were critically ill with exacerbations of acute disseminated lupus erythematosus [1]; 1 had chronic discoid lupus; 6 were patients with moderately severe hyperthyroidism, and the remaining 13 had various other collagen diseases (table 1). The results in the patients with thyrotoxicosis will be presented elsewhere. This report will be limited to our experience with acute disseminated lupus erythematosus.

TABLE 1.—*Number of Patients Treated with Cortisone and ACTH*

| Diagnosis | No. of Patients |
|---|---|
| Disseminated lupus erythematosus | 14 |
| Hyperthyroidism | 6 |
| Polyarteritis nodosa | 2 |
| Rheumatoid arthritis | 3 |
| Dermatomyositis | 1 |
| Nephrotic syndrome | 1 |
| Chronic glomerulonephritis | 1 |
| Loeffler's syndrome | 1 |
| Pemphigus | 1 |
| Scleroderma | 1 |
| Discoid lupus | 1 |
| Active rheumatic fever | 2 |
| | 34 |

From the medical services of the Mount Sinai Hospital.

The cortisone and ACTH were provided by grants from the United States Public Health Service and the New York Foundation.

1. Baehr, G., and Soffer, L. J.: Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin, Bull. New York Acad. Med. **26**:229, 1950. Soffer, L. J.; Boas, N. F.; Levitt, M. F.; Gabrilove, L. J., and Baehr, G.: The Influence of Cortisone and Adrenocorticotropin in Disseminated Lupus Erythematosus, Tr. A. Am. Physicians, to be published.

The diagnosis of acute disseminated lupus erythematosus was based on the characteristic clinical association of fever, weakness, joint pains, typical lesions of skin and mucous membrane, evidence of pleuropericardial involvement and retinal and renal changes. Several patients manifested severe muscle wasting. All patients demonstrated the characteristic laboratory findings, which included microscopic hematuria, leukopenia, anemia, hyperglobulinemia, elevated erythrocyte sedimentation rate and the presence of characteristic lupus cells in both the heparinized bone marrow and the peripheral blood (table 2). Of the 14 patients

TABLE 2.—*Frequency of Clinical Manifestations in Fourteen Patients with Acute Disseminated Lupus*

| Clinical Manifestation | No. of Patients | Result of Treatment |
|---|---|---|
| Fever | 14 | Disappeared within 2 to 4 days |
| Joint symptoms | 14 | Disappeared within 7 days |
| Cachexia | 5 | Improved slowly |
| Erythematous "butterfly" lesion | 7 | Faded slowly during first 2 to 4 wk. of treatment |
| Mucous membrane lesions | 4 | Disappeared after 7 days of treatment |
| Organic psychosis | 2 | Subsided after 3 to 6 days of treatment |
| Raynaud phenomenon | 2 | Subsided after 4 days of treatment |
| Pericardial effusion | 3 | Disappeared after 1 to 3 wk. of treatment |
| Pleural effusion | 4 | Disappeared after 7 to 14 days of treatment |
| Retinal changes | 5 | Improved in 4 patients after 7 to 14 days of treatment |
| Renal abnormalities | 5 | Persisted in all patients |
| L. E. cells | 14 | Persisted in 13 patients |
| Anemia | 14 | Persisted in all patients |
| Leukopenia | 10 | Persisted in 6 patients |
| Thrombocytopenia | 7 | Persisted in all patients |
| Elevated sedimentation rate | 14 | Decreased in 10 patients but returned to normal levels in only 4 |

treated, 11 were females ranging in age from 13 to 55 years and 3 were males ranging from 13 to 51 years of age.

## CLINICAL RESPONSE

Six of the 14 patients were first treated with cortisone to establish a remission and were then treated with ACTH. In 1 patient treatment was started with ACTH and later changed to cortisone. Five were treated exclusively with ACTH and 2 exclusively with cortisone.

The initial dosage of cortisone was 150 to 200 mg. daily and that of ACTH 100 to 150 mg. With both agents the daily amount was divided into four doses. The qualitative response to the two hormones was identical, with prompt defervescence, disappearance of the toxicity and subsidence of the joint pains. The major difference in the effects of the two therapeutic agents was the time interval between the beginning of therapy and the clinical response (fig. 1). With cortisone, two to four days were required before the effects of therapy became evident. The

response to ACTH was more dramatic. A fall in temperature to normal levels and subjective improvement were noted within twelve to eighteen hours after the first injection. This difference in the behavior of the two agents was also apparent after the cessation of therapy. Symptoms and signs recurred five to six days after the discontinuance of treatment with cortisone, whereas clinical relapse following discontinuance of ACTH therapy often occurred within twenty-four hours.

With both cortisone and ACTH the temperature attained normal levels within one to three days. Tachycardia and gallop rhythm usually disappeared by the fourth day and the joint swellings and pain a day or two later. In 7 patients with clinical and roentgenologic evidence of pleural or pericardial involvement, all signs gradually subsided within

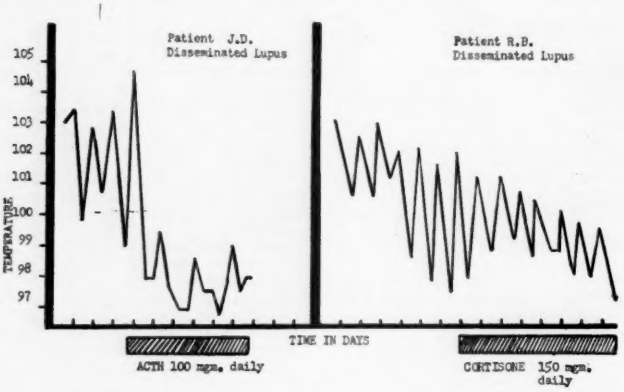


Fig. 1.—Comparison of effect on body temperature of therapy with cortisone and with ACTH.

one to three weeks after the beginning of treatment. The lesions of the mucous membrane disappeared within seven to ten days, although the typical butterfly facial rash responded more slowly. The latter lesions first lost their bright erythematous color, then became irregularly pigmented and finally faded over a period of one to two months. Complete resolution of the characteristic hemorrhages and exudates in the eyegrounds occurred in 4 of 5 patients after two to three weeks of treatment (table 2).

The disease in only 1 patient failed to respond promptly to an intensive course of therapy with cortisone, with dosages as high as 200 mg. daily. The temperature fell slowly and hovered above normal for ten days; tachycardia and gallop rhythm persisted for seven days, and overall clinical response was poor. Since it was suspected that an independent

infection was responsible, the patient was treated actively with antibiotics. After moderately good control for a five week period, the patient had pneumonia of the upper lobe of the left lung and died six weeks after the beginning of therapy. At postmortem examination an extensive pulmonary fungous infection was observed. The failure to respond to adequate treatment with cortisone or ACTH should, therefore, suggest the possible existence of an intercurrent disease process.

With continued therapy there occurred a progressive increase in strength and general well-being. In 10 of the 14 patients in our series, the erythrocyte sedimentation rate gradually fell during the first four to six weeks of treatment, although it reached normal values in only 4 instances. The anemia, however, remained essentially unchanged, and in 2 patients in whom it was particularly prominent transfusions were necessary. The leukopenia tended to disappear in only 4 of the 14 patients. No improvement occurred in the abnormal renal findings in any of the patients. Despite adequate treatment and an otherwise satisfactory clinical response, albuminuria, microscopic hematuria and depressed urea clearance, if present, persisted. One of these patients with particularly severe renal disease and azotemia evidenced a moderate fall in the blood urea nitrogen level during therapy, but the remaining signs of pathologic renal involvement were still present after three months of treatment. In each of the 13 patients in whom lupus cells were consistently noted prior to therapy, this abnormality persisted throughout treatment, although the cells tended to be fewer in number. In one patient the lupus cells were not observed until four days after the beginning of treatment and then subsequently disappeared.

### DOSAGE

After the disease has been under control for several weeks, the daily dosage of cortisone or ACTH is reduced by small decrements every few days until that minimal dosage level is established which maintains the patient in remission. Further reduction will usually be followed by a flare-up of the clinical manifestations of the disease. This minimal maintenance level can be more accurately gaged with ACTH because of the relatively prompt exacerbation which follows inadequate dosage.

Six patients were treated with cortisone for two to four weeks in order to establish a clinical remission. ACTH was then substituted in progressively reduced amounts, with a view to the eventual cessation of all treatment. Of 6 patients thus treated it was possible to discontinue therapy in only 1. This patient had been critically ill, but it was possible to discontinue treatment after a three month period. Three months later, however, she suffered a relapse, which again promptly responded to treatment with ACTH. Of the remaining 5 patients it has been possible

to reduce the minimal maintenance dosage of 2 but impossible to discontinue therapy completely for any. In 2 patients attempts were made to maintain the remission with cortisone injections given on alternate days. In both, the clinical manifestations recurred. Subsequent daily treatment with either cortisone or ACTH again induced a therapeutic response, although the maintenance dosage for ACTH was now observed to have increased.

Six patients were treated with ACTH alone. In none could therapy be completely discontinued without a subsequent return of the symptoms. In 1 instance the required maintenance dosage increased during treatment, and it became necessary to substitute cortisone for long term control.

Two patients were treated solely with cortisone. One had epileptiform convulsions after eighteen days of therapy and all treatment was

TABLE 3.—*Side Effects of Treatment with Cortisone and ACTH*

| Complication | No. of Cases | Complication | No. of Cases |
|---|---|---|---|
| Hypertension | 10 | Hirsutism | 5 |
| Edema | 8 | Striae | 3 |
| Depression | 6 | Congestive heart failure | 4 |
| Pigmentation | 5 | Alkalosis | 5 |
| Convulsions | 4 | Diabetes mellitus | 1 |

necessarily stopped. The second patient has been under treatment with a gradually decreasing dosage, but she still requires 50 to 75 mg. a day.

### UNTOWARD EFFECTS OF THERAPY

The course of therapy in acute disseminated lupus erythematosus is further complicated by a series of side effects and complications which become an intrinsic part of the management of the disease (table 3).

*Weight Gain and Edema.*—Ten patients gained approximately 10 to 20 pounds (4.5 to 9.1 Kg.) during the first two to three weeks of therapy. The initial gain in weight was so abrupt as to suggest a rapid accumulation of fluid. Eight of the 10 patients showed visible edema of the flanks, buttocks and legs. It was of some interest that the degree of gain in weight could not always be correlated with the prominence of the edema. In 2 instances the severity of the edema progressed despite the absence of any simultaneous gain in weight. The degree of weight gain and the subsequent development of edema were in part conditioned by the salt content of the diet. Twelve patients were, therefore, maintained on salt-free diets (8.5 milliequivalents of sodium a day) throughout the period of therapy. Unpredictable departures from the salt-free diet could usually be detected by a sudden increase in weight. Eight

patients needed one or more intramuscular injections of meralluride (mercuhydrin®) sodium solution to control the fluid retention. After the acute weight gain which occurred early during the course of therapy, the patients continued to gain weight more slowly. This was considered to be a reflection of the increased appetite and food intake rather than of further fluid retention.

*Hypertension.*—During the course of treatment, 10 patients displayed an increase in the systolic and diastolic blood pressures, particularly in the first month of therapy. In 3 of these patients the rises were of moderate degree, with an increase in systolic and diastolic blood pressures, respectively, of 50 to 80 and 20 to 40 mm. of mercury. In the remaining 7 patients the increases in blood pressure were only slight. In most instances the maximum rise in blood pressure occurred before the maximum gain in weight. In 2 patients, however, they occurred simultaneously. After the administration of meralluride to these 2 patients, there followed a simultaneous fall in total body weight and arterial blood pressure. Although the restriction in the daily salt intake did not eliminate the rise in blood pressure, it did lessen the degree of elevation. As therapy was continued and the dosage of either hormone progressively reduced, the elevated blood pressure tended to fall.

*Congestive Heart Failure.*—Four of the patients had acute congestive heart failure during treatment. In 1 patient acute pulmonary edema supervened on two different occasions, one while he received cortisone and the other during ACTH therapy. In both instances these attacks occurred simultaneously with maximum increases in weight and blood pressure. In a second patient the congestive failure was evidenced by a sudden enlargement of the liver and rise in venous pressure after a gain of 3 pounds (1.3 Kg.) in weight during eight days of cortisone treatment. The third and fourth instances of heart failure occurred in 2 patients after nine and ninety days of ACTH therapy, respectively. These episodes were similarly associated with only a minimal gain in weight. The attacks were readily controlled with administration of meralluride, oxygen and digitalis, and it was possible to continue treatment in all but 1 patient. The frequency of this complication in our group probably reflects the diffuse involvement of the cardiovascular system in acute disseminated lupus erythematosus.

*Alkalosis.*—During the course of therapy 7 patients showed mild alterations in their serum electrolyte pattern, as evidenced by a slight decrease in serum chloride, a slight rise in carbon dioxide content and, in 4 instances, mild hypokalemia. However, in 5 patients in whom injections of meralluride were used to accelerate the loss of retained fluid or to control the symptoms of congestive heart failure, the mild preexisting alkalosis was intensified. In the one patient who had acute

pulmonary edema on two occasions, the injections of meralluride were followed not only by a prompt and profuse diuresis but also by a rise in serum carbon dioxide content to 42, a fall in serum chloride to 78 and a fall in serum potassium to 1.9 milliequivalents per liter. The increase in the carbon dioxide content with the reciprocal fall in serum chloride persisted unless corrected by the daily ingestion of 6 to 8 Gm. of potassium or ammonium chloride. It should be emphasized that the hypertension, fluid retention, congestive heart failure and the subsequent mercurial alkalosis can usually be corrected without discontinuing treatment. These complications tend to occur less often as therapy is prolonged.

*Mental Changes.*—Nine patients showed a general improvement in mood coincidental with the disappearance of the weakness, the distressing joint pains and the high fever. They were more cheerful and alert and even mildly euphoric. It was the impression of the clinical observers that, for the most part, this change in affect was secondary to the general systemic improvement. However, in 6 patients the alteration in mood was much more striking and was characterized by severe depressions and apathy. In one patient there were episodes of severe depression, alternating with periods of elation, euphoria and manic outbursts. These changes appeared after seven days of treatment with cortisone and then gradually subsided during a two month period of continued treatment. In another instance a patient displayed a severe reactive depression during the first weeks of therapy with cortisone. This patient manifested pronounced apathy, incontinence of urine and stools, loss of voice, visual and auditory hallucinatory phenomena and even threats of suicide. This reaction similarly subsided despite the continuance of therapy. Three patients had milder and transient depressions during the first week of treatment with ACTH. One patient demonstrated hostility and taciturn rejection of the entire staff for two months. It was considered likely that these various personality changes represented an exaggeration of preexisting traits. Three critically ill patients, who had acute toxic psychoses as a manifestation of the disease process, showed progressive improvement in the mental state after five to six days of treatment with either cortisone or ACTH.

*Convulsions.*—Four patients had convulsive episodes during the course of therapy. In one instance there were three generalized epileptiform clonic and tonic convulsions after three weeks of treatment with cortisone. In another patient convulsions developed after eight days of therapy with ACTH. During this period the general clinical response had been satisfactory. Despite the cessation of treatment and the use of anticonvulsant measures, the patient exhibited status epilepticus, became comatose and died two days after the onset of the first convulsion and

eleven days after the beginning of ACTH therapy. In 2 other instances convulsions occurred after treatment with ACTH for ten and sixteen days, respectively. The hormone therapy was interrupted for two to three days, but when evidence of recurrence of the disease developed treatment was again instituted with the precautionary use of diphenylhydantoin (dilantin®) sodium and phenobarbital. One of these patients died two weeks later of an intercurrent fungous infection of the lung, but the other has since been maintained on ACTH therapy with no further convulsions.

The frequency of convulsive seizures in untreated acute disseminated lupus was first emphasized by Klemperer, Pollack and Baehr,[2] who noted this complication in 6 to 20 patients. In each instance, however, these seizures represented a terminal manifestation.

Electroencephalograms are so often abnormal during the acute stage of acute disseminated lupus that they were of little help in predicting the onset of convulsions.

*Electrocardiographic Changes.*—During continued treatment with cortisone or ACTH, serial electrocardiographic studies showed progressive increases in the Q-T intervals, with inversion of the T waves. Although tachycardia, fever, pericardial effusion, pleurisy and anemia complicated the pretreatment records, the aforementioned changes occurred consistently. In one patient, during the first ten days of therapy with cortisone, two transient episodes of auricular fibrillation occurred, both of which subsided spontaneously. In another patient, pronounced sinus bradycardia developed soon after the beginning of treatment with ACTH. The bradycardia persisted for almost five days and without specific therapy changed suddenly into auricular fibrillation with complete heart block. These changes gradually reverted to a regular sinus rhythm, despite the continuation of treatment.

*Skin Changes.*—The most consistent changes observed were a fullness of the face, rounding of the facial contour and a bloated, often plethoric, appearance. These changes became evident several days after the beginning of hormone treatment but subsided somewhat as the dosages were reduced. Four of the 12 female patients showed miliary acneform eruptions of the face, neck, back and chest. These lesions, too, regressed as the dosage was progressively reduced.

Pinkish striae appeared in 3 patients after ten, twelve and nineteen days of treatment. These were localized to the flanks, breasts and upper outer aspects of the arms. The striae progressed during treatment, but there has been no opportunity to observe whether they persist after therapy is discontinued.

2. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941.

Five of the female patients exhibited a scanty, downy hirsutism involving the face, upper arms and back. This hair growth appeared only after one to two months of treatment and gradually disappeared in the one patient in whom therapy was discontinued.

Five patients had a diffuse brown pigmentation of the face, arms and legs after two to three months of treatment. Two of these patients received ACTH alone and 3 a short course of cortisone therapy followed by ACTH administration. There was some pigmentation of the mucous membranes, palmar creases and scars. In no instance has therapy been discontinued for a long enough time to evaluate the permanence of these changes. This diffuse pigmentation differs from the irregular brownish discolorations which developed in each of the typical skin lesions soon after therapy was begun. The latter changes were limited to the sites of the previously erythematous lesions and probably represented the breakdown and reabsorption of the pigment derived from the red blood cells exuded during the active stage of the disease.

*Diabetes.*—Frank diabetes mellitus occurred during treatment in 1 of the 14 patients. This was a 51 year old man whose fasting blood sugar levels were repeatedly normal before and during the first two weeks of treatment. After eighteen days of therapy with cortisone and three days with ACTH he showed polydipsia, polyuria and a weight loss of 12 pounds (5.4 Kg.) despite a ravenous appetite. The fasting blood sugar level had now risen to 300 mg. per hundred cubic centimeters, and the daily urinary excretion of glucose varied from 150 to 250 Gm. With the daily administration of 60 mg. of ACTH, 120 units of regular insulin a day was required to reduce the glycosuria to 25 to 35 Gm. The day after the beginning of treatment with insulin, the urinary nitrogen loss was almost halved and thereafter a progressive improvement in the symptoms occurred. During the course of the next three months the gradual reduction in the daily dosage of ACTH was associated with a decrease in the insulin requirements. At present with the daily administration of 10 mg. of ACTH he still requires 30 units of insulin. It is of interest that this patient had a family history strongly positive for diabetes.

### BIOCHEMICAL EFFECTS OF THERAPY

*Body Water and Electrolyte Changes.*—Balance studies were performed in order to elucidate the mechanism whereby edema or congestive heart failure may develop without significant gain in weight in patients given cortisone or ACTH therapy. Patient F. W. was maintained on a daily salt-free diet which contained 5 milliequivalents of sodium, 130 milliequivalents of potassium, 42 milliequivalents of chloride, 2.1 Gm. of calcium, 1.7 Gm. of phosphorus and 7.5 Gm. of protein

nitrogen. After 2 three day control periods, he was given 150 mg. of cortisone daily for nine days, divided into 3 three day periods. Fluid and electrolyte intake and output, plasma volume and extracellular volume (inulin space) were measured and followed serially. The results of this study are presented in figures 2 and 3.

During the six days of cortisone therapy, there occurred no weight gain and the patient remained in water, sodium, potassium and chloride equilibrium. There was a moderately negative calcium and nitrogen balance. Serial measurements of the inulin space, however, demonstrated an increase of approximately 4,500 cc. in isotonic extracellular fluid volume, with a proportionately smaller increase in plasma volume. The great increase in extracellular fluid volume, with the consequent

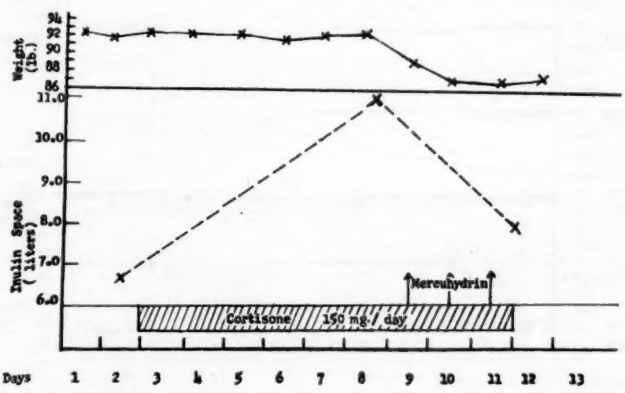


Fig. 2.—Influence of administration of cortisone and meralluride (mercuhydrin®) sodium solution on extracellular volume and body weight.

increase in extracellular sodium and chloride, in the absence of an overall positive sodium, chloride or water balance, indicates that the short term cortisone therapy in this patient produced a shift of water, sodium and chloride from within the cells outward. This shift of water into the extracellular compartment has been previously demonstrated in dogs receiving desoxycorticosterone acetate.[3] The simultaneous negative calcium balance implies that a part of the extracellular sodium increment may derive from the bones.

That such an augmented extracellular fluid volume may develop in a patient maintained on a salt-free diet explains the frequency with

3. Gaudino, M., and Levitt, M. F.: The Influence of the Adrenal Gland on Body Water and Renal Function, J. Clin. Investigation **38**:1487, 1949.

which edema is encountered in unrestricted patients receiving cortisone. It is likely that congestive heart failure ensues only when the progressive increase in extracellular fluid volume is reflected in a significant increase in the plasma volume.

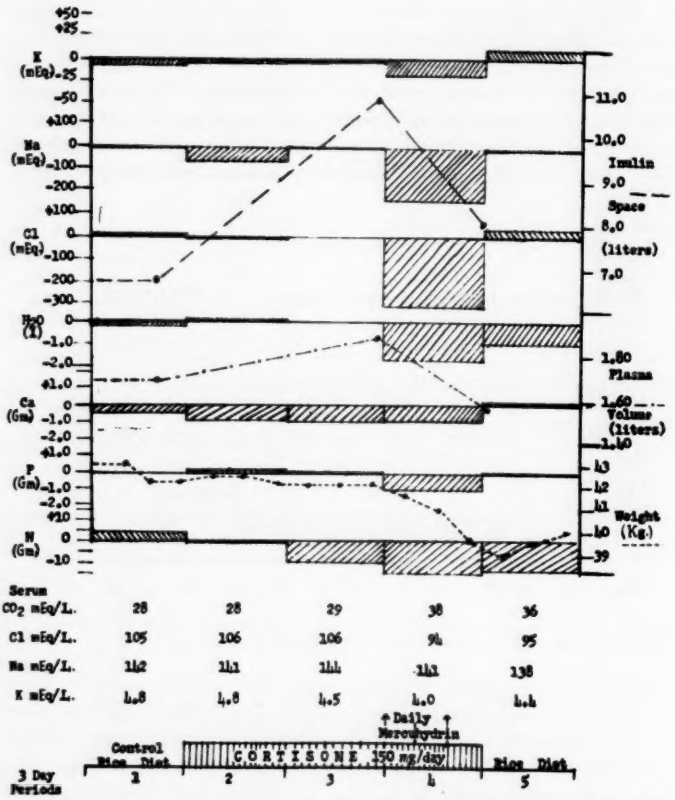


Fig. 3.—Balance study on patient F. W. with lupus erythematosus. Effect of administration of cortisone and meralluride sodium solution during a salt-free diet.

The characteristic exaggeration of the alkalosis which follows meralluride therapy was studied in two balance experiments. The data are presented from one patient (F. W.) to whom meralluride was administered daily during the third three day cortisone period (figs. 2 and 3). In both instances the diuretic produced a definite chloruresis, accom-

panied with a less distinct sodium loss and only a mild and inconstant potassium loss. In each case the fall in extracellular sodium (measured by the product of the inulin space and the serum sodium concentration) was greater than the concomitant sodium diuresis, indicating a shift of sodium back into the cells or possibly the bone. It appears likely that the exaggeration of the alkalosis following the administration of meralluride is a consequence of the proportionately greater urinary loss of chlorides. The minimal potassium loss which occurred does not appear adequate to account for the hypochloremic alkalosis. The significance of the shift of sodium out of the extracellular compartment is obscure.

*Carbohydrate Metabolism.*—Of the 14 patients treated, only 1 displayed frank diabetes. In 4 others there was a transient slight increase

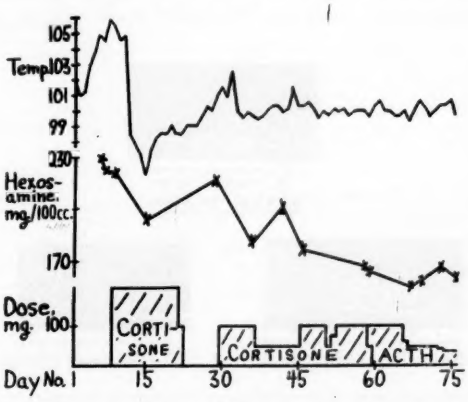


Fig. 4.—Serum hexosamine levels during the course of cortisone and ACTH therapy.

in fasting blood sugar levels, in none great enough to produce glycosuria. Dextrose tolerance curves were followed serially in 3 patients but no alterations were noted.

*Serum Glucosamine.*—Boas and Soffer [4] have followed the serum hexosamine levels in the patients receiving treatment. The serum hexosamine is believed to be derived from the mucopolysaccharides of the connective tissue ground substance, which is characteristically altered and increased in acute disseminated lupus erythematosus. The normal serum level varies from 100 to 120 mg. per hundred cubic centimeters.

4. Boas, N., and Soffer, L. J.: The Effect of Adrenocorticotropic Hormone and Cortisone on Serum Hexosamine Levels in Disseminated Lupus Erythematosus, to be published.

In acute disseminated lupus erythematosus the serum hexosamine usually varies between 180 and 220 mg. per hundred cubic centimeters. Under the influence of therapy with cortisone or ACTH there is a transient rise during the first two days of treatment, followed by a slow, progressive fall toward normal as long as clinical improvement is maintained. Clinical recurrence of the illness is promptly followed by a conspicuous rise in the serum hexosamine level, and its fluctuations parallel the clinical course with remarkable consistency (fig. 4).

*Blood Proteins and Lipids.*—The characteristic serum electrophoretic pattern in acute disseminated lupus, as demonstrated by Coburn and Moore [5] and by Reiner,[6] consists of a relatively normal serum total protein, a decrease in the albumin fraction, normal alpha$_1$ and beta globulin fractions and a considerable increase in alpha$_2$ and gamma globulin. During treatment with cortisone and ACTH there occurred a progres-

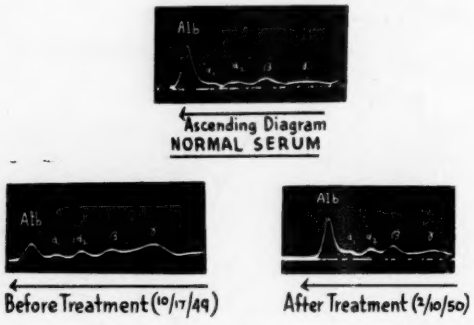


Fig. 5.—Electrophoretic pattern of serum proteins in a patient (M. F.) with acute disseminated lupus before and after treatment with cortisone and ACTH.

sive increase in the serum albumin fraction and a pronounced decrease in the gamma globulin. The alpha$_2$ globulin, however, remained elevated. These changes were obvious after one to two weeks of treatment and progressed as therapy was continued (tables 4 and 5; fig. 5).

Adlersberg, Schaefer and Dritch [7] demonstrated on our patients an increase in total serum phospholipids during treatment. The amount

5. Coburn, A. F., and Moore, D. H.: The Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**:196, 1943.

6. Reiner, M.: The Effect of Cortisone and Adrenocorticotropin Therapy on Serum Proteins in Disseminated Lupus Erythematosus, Proc. Soc. Exper. Biol. & Med., to be published.

7. Adlersberg, D.; Schaefer, L. E., and Dritch, R.: Effect of Cortisone, Adrenocorticotropic Hormone (ACTH), and Desoxycorticosterone Acetate (Doca) on Serum Lipids, J. Clin. Investigation, to be published.

of neutral fat, however, was not significantly altered, and the blood cholesterol and cholesterol esters tended to rise slightly.

*Urinary Steroids.*—Under the influence of cortisone treatment the urinary excretion of the 11-oxygenated steroids increased slowly over a period of seven to ten days, but no increase occurred in the urinary excretion of the neutral 17-ketosteroids. With ACTH therapy there

TABLE 4.—*Summary of Electrophoretic Distribution of Serum Proteins in Disseminated Lupus Erythematosus*

| | Total Protein, Gm./100 Cc. | Albumin to Globulin Ratio | Relative per Cent of Total Proteins | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Globulins | | | |
| | | | Albumin | Alpha$_1$ | Alpha$_2$ | Beta | Gamma |
| Normal (average of 60 cases) | 7.22 | 1.3 | 56.8 | 7.2 | 8.7 | 12.8 | 14.4 |
| Untreated disseminated lupus erythematosus (average of 18 cases) | 6.94 | 0.5 | 34.5 | 7.2 | 15.6 | 12.9 | 29.8 |

TABLE 5.—*Summary of Serum Protein Distribution in Five Patients with Disseminated Lupus Erythematosus Before and After Treatment with Cortisone and ACTH*

| | Total Protein, Gm./100 Cc. | Albumin to Globulin Ratio | Relative per Cent of Total Proteins | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Globulins | | | |
| | | | Albumin | Alpha$_1$ | Alpha$_2$ | Beta | Gamma |
| Before treatment | 7.07 | 0.6 | 34.7 | 8.1 | 12.5 | 15.1 | 29.6 |
| After treatment | 6.11 | 0.8 | 43.9 | 7.2 | 12.7 | 16.6 | 19.5 |

TABLE 6.—*Effect of Administration of Cortisone and of ACTH on the Urinary Excretion of Neutral 17-Ketosteroids and 11-Oxygenated Steroids**

| | No. of Patients Treated | Average Daily Urinary Excretion of Neutral 17-Ketosteroids Before Therapy | During Height of Therapy | Average Daily Urinary Excretion of 11-Oxygenated Steroids Before Therapy | During Height of Therapy |
|---|---|---|---|---|---|
| Cortisone | 5 | 5.94 | 6.32 | 2.01 | 9.80 (7 to 10 days) |
| ACTH | 5 | 7.0 | 13.9 | 1.71 | 6.50 (24 hr.) |

* Measured in milligrams per twenty-four hour volume of urine.

occurred a prompt increase in urinary excretion of both the 11-oxygenated steroids and the neutral 17-ketosteroids (table 6).

## COMMENT

The clinical results obtained in the treatment of acute disseminated lupus erythematosus with both cortisone and ACTH are striking. It must be emphasized, however, that although these agents are capable of inducing clinical remissions they do not effect a cure of the underlying disease process. The postmortem examination of 2 patients who

had been treated intensively failed to show any histologic changes that were in any way different from those observed in patients with untreated lupus. Of the 14 patients reported on in this series, 11 responded well in that the acute manifestations of the disease promptly subsided and the patients became comfortably ambulatory. However, the characteristic lupus cells, the anemia, the thrombocytopenia and the abnormal renal findings persisted, and only infrequently did the sedimentation rate return to normal levels. In only one of this group could treatment be discontinued temporarily after three months of therapy. The remaining 10 patients still require continuous treatment after periods which vary from one to seven months. Three patients in this series died. In one, death occurred because of inadequate therapy, in another because of repeated convulsions and in the third as a result of an intercurrent infection.

It is perhaps too early to evaluate the ultimate results. The present indications are that in most instances treatment must be continued indefinitely or until such time as a spontaneous remission occurs. Long term treatment poses the problem of coping with the side effects induced by both ACTH and cortisone. The more serious ones, such as edema and congestive heart failure, can be prevented to some degree by the rigid restriction of salt intake. A rapid gain in weight is an indication of fluid retention and should be countered with administration of mercurial diuretics. The subsequent alkalosis must be watched for and properly corrected. Convulsive seizures constitute an imposing problem. However, they have not prevented further treatment after a suitable period of rest and reduction in the dosage of the hormones. The convulsive episodes have occurred either relatively early in the course of therapy or not at all. Hirsutism, acne, rounding of the contours of the face, diffuse pigmentation and striae occur often and will persist only as long as treatment is continued. Diabetes occurs infrequently and is controlled with difficulty. The daily amount of insulin which is required for control of the diabetes bears a direct relationship to the dosage of hormone used.

It should be emphasized that the hazards encountered in the treatment of acute disseminated lupus with either cortisone or ACTH are perhaps greater than those observed when these agents are used in the therapy of other illnesses. This is probably due to the fact that disseminated lupus is a diffuse disease process which may seriously involve such vital organs as the heart, kidneys and brain.

## SUMMARY

Treatment with cortisone and with ACTH produces prompt and striking remissions in the clinical manifestations of acute disseminated lupus erythematosus.

The persistence of the lupus cells, abnormal urinary signs, leukopenia, thrombocytopenia and pathologic alterations at postmortem examination suggest that therapy with these hormonal fractions does not primarily alter the disease process, although it induces clinical remissions.

The exacerbations which follow attempts to discontinue therapy indicate that long range or even permanent treatment may be necessary to control the disease.

The treatment of acute disseminated lupus with cortisone or ACTH may be complicated by frequent untoward side effects. However, with careful clinical observation these effects may be minimized and corrected and therapy continued.

# Case Reports

## POLYNEURITIS

### Complete Pharyngeal and Respiratory Paralysis with Recovery

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SPRINGFIELD, MO.

Among the neurologic disorders classified as "polyneuritis" are those falling into a rather large group which is most commonly referred to as the Guillain-Barré syndrome. Guillain and his associates first published their observations in 1916.[1] Since that time numerous reports of similar illnesses have been published under a wide variety of names. A partial list includes: myeloradiculitis,[2] acute infective polyneuritis,[3] infective neuronitis,[4] acute febrile polyneuritis,[5] acute encephalomyeloradiculoneuritis [6] and polyradiculoneuritis.[7] As a group they are distinguished by their involvement of the peripheral nerves and excellent prognosis. Confusion in terminology has existed because of the failure to demonstrate a single etiologic agent and because of the lack of agreement concerning the existence of definitive syndromes among the group. Hand and Rudoy [8] were of the belief that the Guillain-Barré syndrome is a clinical entity in which albuminocytologic dissociation in the spinal fluid is characteristically observed. Although the variety of names indicates the protean nature of the illness, its manifestations fall into the same general pattern.

The disease is described by Brain [9] as most commonly following a febrile illness with a latent period of days to weeks. The paralytic symptoms are frequently of sudden onset and may affect all four limbs and the trunk and facial muscles. Dysphagia from pharyngeal paralysis is not uncommon. Pain, tingling and numbness occur in the affected muscles. Muscular atrophy is unusual, and recovery may take place completely or in part. The spinal fluid is described as showing an absence of cells in the presence of an elevated protein level, although completely normal spinal fluid has also been reported.[10]

1. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462, 1916.

2. Strauss, I., and Rabiner, A. M.: Myeloradiculitis: Clinical Syndrome, with Report of Seven Cases, Arch. Neurol. & Psychiat. **23**:240 (Feb.) 1930.

3. Bradford, J. R.; Bashford, E. F., and Wilson, J. A.: Acute Infective Polyneuritis, Quart. J. Med. **12**:88, 1918.

4. Kennedy, F.: Infective Neuronitis, Arch. Neurol. & Psychiat. **2**:621 (Dec.) 1919.

5. Holmes, G.: Acute Febrile Polyneuritis, Brit. M. J. **2**:37, 1917.

6. Mackay, R. P.: Acute Encephalo-Myelo-Radiculoneuritis (Guillain Barré Syndrome), M. Clin. North America **1**:8, 1945.

7. Lowenberg, K., and Foster, D. B.: Polyradiculoneuritis with Albuminocytologic Dissociation: Pathoanatomic Report of 3 Cases, Arch. Neurol. & Psychiat. **53**:185 (March) 1945.

8. Hand, M., and Rudoy, M.: The Prognostic Significance of the "Guillain-Barré Syndrome," Ann. Int. Med. **29**:91, 1948.

9. Brain, W. R.: Diseases of the Nervous System, ed. 2, Oxford Medical Publications, New York, Oxford University Press, 1940.

10. Bradford.[3] Holmes.[5]

While recovery is one of the distinguishing features of the disease, numerous fatalities have been reported. The fact that the majority of these are due to respiratory paralysis is well borne out by a partial review of the literature (table). Of the 25 deaths indicated in this table, 23 were due to involvement of the muscles of respiration. Despite the serious implication of respiratory paralysis, the degree to which it may occur and yet be followed by recovery is astonishing. The following case is reported as an example of this.

*Report of Fatalities*

| Authors | Cases | Deaths | Cause of Death |
|---|---|---|---|
| Kennedy [4] | 4 | 1 | Loss of swallowing reflex with cyanosis and asphyxiation |
| Bradford, Bradford and Wilson [3] | 20 | 3 | One patient with respiratory failure; one with concurrent Hodgkin's disease; no details were given on the remaining patient |
| Holmes [5] | 12 | 2 | Paresis of respiratory movements a contributing factor |
| Lowenberg and Foster [7] | 3 | 3 | Pulmonary infection and respiratory paralysis |
| Gilpin, S. F.; Moersh, F. P., and Kernohan, J. W.: Arch. Neurol. & Psychiat. **35**: 937 (May) 1936 | 30 | 8 | Respiratory failure |
| Taylor, E. W., and McDonald, C. A.: Arch. Neurol. & Psychiat. **27**: 79 (Jan.) 1932 | 16 | 1 | Respiratory failure |
| Shaskan, D.; Teitelbaum, H. A., and Stevenson, L. D.: Arch. Neurol. & Psychiat. **44**: 599 (Sept.) 1940 | 7 | 1 | Respiratory failure |
| Lewey, F. H.: J. Pediat. **26**: 165, 1945 | 2 | 1 | Respiratory failure |
| Roseman, E., and Aring, C. D.: Medicine **20**: 463, 1941 | 16 | 3 | Respiratory involvement |
| Garvey, P. H., and Slavin, H. B.: Internat. Clin. **4**: 38, 1938 | 5 | 2 | Respiratory paralysis |
| Totals | 115 | 25 | |

REPORT OF A CASE

*History.*—J. G., a 50 year old man, entered Burge Hospital, Springfield, Mo., on March 20, 1950, complaining of generalized weakness of twelve hours' duration. A week prior to his admission he had a mild sore throat lasting three days. Two days before admission he noticed a tingling sensation in the stump of his left leg, the site of a previous high thigh amputation. The following day he felt well and was quite active doing work about the house. That evening he found that his hands were unusually clumsy, and because of a feeling of fatigue he went to bed early. On awakening the next morning, after sleeping soundly, he found that he could move only with great effort, sitting up on the side of the bed with difficulty. He felt entirely well otherwise, with no malaise, headache or muscular pains. Hospitalization was arranged, and on his arrival, two hours after waking, the paralysis had progressed to the point where he had only slight motion of the extremities.

*Past History.*—At the age of 30 the patient had a keloid develop just distal to the left knee. After several operations and extensive roentgen therapy, malignant changes developed, requiring a high thigh amputation. Other than this no serious illness or injury had taken place.

*Results of Physical Examination.*—The patient was a large man, weighing 200 pounds (90.7 Kg.), unable to move and sweating freely. There were no skin lesions. Except for the amputation the bones, joints and muscles were normal. No lymphadenopathy was present. No abnormalities were noted in the ears, nose and throat. The pupils were equal and active, and the optic disks were normally cupped. The retinal vessels showed grade 1 arteriovenous compression. The neck was supple. The lungs were clear to auscultation and percussion. The pulse rate was 80 and the blood pressure 220 systolic and 130 diastolic. The heart appeared to be slightly enlarged to percussion. There were no murmurs. No abdominal tenderness was noted, and no palpable organs or masses were felt. The rectal examination gave essentially normal results.

Neurologic study showed the following changes: There was loss of sensation to light touch and pinprick in a patchy distribution over both arms, bilaterally to the level of the eighth dorsal vertebra over the back and over somewhat irregular areas of the anterior wall of the chest. Subjectively, the patient was complaining of tingling and numbness of the hands and feet. The arms and leg could be rotated and moved back and forth across the bed but could perform no work against gravity. The fingers could be moved but not against resistance. The thoracic muscles were functioning satisfactorily, and the head could be lifted. The triceps, biceps and radial reflexes were diminished in the right arm and absent in the left. The knee and ankle jerks were present on the right, and the Babinski reflex showed a plantar response. No abnormalities of the cranial nerves could be demonstrated.

*Laboratory Data.*—The hemoglobin concentration was 14.6 Gm. per hundred cubic centimeters. The white blood cell count varied from 11,500 to 21,000, with persistent eosinophilia of 4 to 10 per cent in the differential count. The urine consistently showed a trace of albumin and on one occasion a 1 plus reaction for sugar. On his admission the nonprotein nitrogen was 48 mg., later rising to 70 mg. and finally returning to 35 mg. per hundred cubic centimeters. The fasting blood sugar level was 143 mg. per hundred cubic centimeters. Serum chloride measured 480 mg. The day following his admission to the hospital a lumbar puncture obtained clear, colorless liquid. The initial pressure was 200 mm. of water. The fluid showed 87 mg. of sugar and 40 mg. of protein per hundred cubic centimeters, negative Kahn and Pandy reactions and a colloidal gold reaction of 1122211210.

*Course.*—During the first twenty-four hours in the hospital, the patient's deep reflexes and abdominal reflexes disappeared, with an accompanying complete flaccid paralysis of the muscles of the extremities. By the afternoon of the second day in the hospital there was obvious weakness of the thoracic muscles, with breathing becoming largely diaphragmatic; at about the same time severe muscular aching developed in his back and extremities. He was then placed in a respirator, adjusting to it without dfifficulty. On the third hospital day swallowing became difficult, and within a few hours pharyngeal paralysis had progressed to the point where it was complete. When the respirator was stopped for five minutes, only feeble and spasmodic contractions of the diaphragm occurred. By the fourth hospital day salivation required almost continuous suctioning, and one tracheal plug was removed with difficulty. A tracheotomy was done as an elective procedure, with the patient under local anesthesia and with the use of a chest respirator instead of the standard apparatus. At this time it was noted that while the patient slept there was little or no oral secretion; sedation with sodium phenobarbital was used freely to take advantage of this and reduce the trauma of frequent suction. Fluids were given intravenously as required. On the eighth hospital day it was thought the patient could produce faint swallowing motions; by the tenth hospital day he could move his fingers, and thereafter muscle control rapidly returned. Fourteen days after being put in the respirator, he was able to breathe without

assistance for one hour. The tracheotomy tube was removed on the seventeenth hospital day. He was left out of the respirator for gradually lengthening periods until the twenty-seventh hospital day, when its use was no longer considered necessary. A supervised physical therapy program was carried out, with gradually increased exercise and mobilization. At the time of his discharge, six weeks after the onset of his disease, the patient was once more walking. Diagnosis on discharge was polyneuritis and essential hypertensive vascular disease. One month after his return home, pain and swelling developed over the metacarpal phalangeal joints bilaterally. The appearance was consistent with acute rheumatoid arthritis, which has since largely subsided. There has been no muscular atrophy, and only slight weakness of the hands has remained, which may be explained by the development of the arthritis. All deep reflexes have returned, and no sensory defects can be demonstrated.

## COMMENT

This case of polyneuritis is considered characteristic enough to be classified with the group designated by the name Guillain-Barré disease. Albuminocytologic dissociation was not demonstrated, but in view of the lack of serial lumbar punctures it cannot be excluded as a possibility. The reversibility of the disease process made it clear that every effort should be used to sustain the patient through the acute phase. Early use of the respirator seemed particularly important. Swank [11] has emphasized this point, presenting evidence to show that waiting until cyanosis and labored breathing occur may allow irreversible atelectasis with almost certain superimposed infection to take place. He suggested the use of the basal metabolism machine to determine the character of the respiration, tidal air and vital capacity as a guide to judging the need for a respirator. In this case the patient was not removed permanently from the respirator until the tidal air was over 400 cc. and the vital capacity had reached 3,000 cc. Despite the satisfactory adjustment of the patient to artificial respiration, atelectasis and pneumonia from aspirated secretions still seemed likely until tracheotomy was performed. After the tracheotomy tube was in place, the airway was kept clear with relatively little difficulty. The value of this procedure is well known to those accustomed to caring for patients with the bulbar type of poliomyelitis.[12]

Reduction of salivation during sleep is a physiologic fact.[13] Advantage was taken of this by heavy sedation during the acute phase of the disease, with a definite decrease in the amount of oral secretion. This not only simplified care of the patient but also eliminated the trauma to the epiglottis, soft palate and posterior pharynx resulting from constant suction. Atropine sulfate was given prior to sedation, and its administration was accompanied with restlessness, tachycardia and discomfort to the point where it could no longer be used. Finally, of prime importance are the constant care and attention of members of the nursing staff.

## SUMMARY

A case is presented of polyneuritis with respiratory paralysis of two weeks' duration and pharyngeal paralysis of six days' duration followed by recovery. Early use of the mechanical respirator, tracheotomy and heavy sedation during the acute phase were valuable aids in management.

11. Swank, R. L.: Respiratory Impairment and Pulmonary Complications in Paralyzed States: A Method for Early Detection, Ann. Int. Med. **32**:229, 1950.

12. Baker, A. B.: Bulbar Poliomyelitis: Its Mechanism and Treatment, Am. J. Med. **6**:614, 1949.

13. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945.

# CHRONIC RECURRENT NONHEMOLYTIC STREPTOCOCCIC ENDOCARDITIS

## Report of a Patient Treated Concurrently with Penicillin and Dihydrostreptomycin

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Relapse of subacute bacterial endocarditis following penicillin therapy has been observed in some patients with all dosage regimens thus far adopted for general use. A significant reduction in the frequency of relapse has been accomplished in recent years by employing larger doses of penicillin and by extending the duration of treatment to six or more weeks. The refractory cases now encountered are frequently those in which the infection is caused by organisms highly resistant to penicillin, notably enterococci. In other cases, in which the organisms are quite sensitive to penicillin in vitro, relapse following the administration of penicillin is not readily attributable to a property of the infecting bacterial population but is generally ascribed to the nature of the lesion or to a deficiency in the resistance mechanisms of the particular host.

Recent observations on the combined action of penicillin and streptomycin on Enterococcus in vitro, together with the favorable results obtained by the concurrent administration of these two drugs to patients with enterococcic endocarditis,[1] have suggested the use of a similar regimen in cases caused by nonhemolytic streptococci of the viridans group which have proved especially refractory to penicillin therapy.

The present report is of a case of nonhemolytic streptococcic endocarditis which had proved exceedingly refractory to prolonged and repeated penicillin therapy. Although suppression of the infection had been readily achieved with each course of penicillin treatment, relapses had occurred repeatedly over a 2½ year period. Arrest of the infection was finally achieved, however, by the concurrent administration of penicillin and dihydrostreptomycin.

### REPORT OF CASE

E. B., a 52 year old white Swiss-born importer, was admitted to the Medical Service of The New York Hospital—Cornell Medical Center on Jan. 11, 1949, with the complaint of "endocarditis" of 2½ years' duration. The patient and his wife

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This study was aided in part by grants from The Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service; Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., and Chas. Pfizer & Company, Inc., Brooklyn.

1. Robbins, W. C., and Tompsett, R.: The Treatment of Enterococcal Endocarditis: Results of the Combined Therapy of 7 Patients, to be published.

were highly intelligent and reliable persons who had kept a detailed record of his illness, from which figures 1 to 3 are derived.

The patient had had diphtheria and scarlet fever at the age of 10 years and had suffered from mild "colitis" for many years. There was no history suggestive of rheumatic fever. A cardiac murmur was first noted on routine physical examination in 1936 and again in 1938.

In May 1946, while visiting Switzerland, the patient experienced the onset of fatigue, malaise, anorexia, morning nausea and daily elevation in temperature to 38 to 40 C. (100.4 to 104 F.). He was hospitalized in June 1946, and the diagnosis of bacterial endocarditis was substantiated by the demonstration of streptococcic bacteremia. The Streptococcus isolated was demonstrated to be quite sensitive to penicillin on in vitro testing. The patient was treated briefly with sulfonamides, followed by three courses of penicillin; he received from 240,000 to 600,000 units daily by intermittent intramuscular injection. This period of treatment extended through nine weeks and resulted in defervescence and in reversal of bacteremia (fig. 1). Fever recurred, however, soon after the discontinuance of penicillin therapy, so that it was resumed on September 24 and continued with a good response until October 7. It was again discontinued, but the patient experienced a prompt rise in temperature, and penicillin treatment was restarted on October 16 and continued for four weeks. Another recurrence, the patient's third, with demonstrable bacteremia, resulted within a week. Administration of penicillin, 1,000,000 units daily, was started on Dec. 1, 1946 and continued through Jan. 21, 1947. Defervescence and symptomatic improvement were definite during therapy, but relapse occurred again soon after penicillin treatment was stopped. From February 9 to April 27, a period of seven weeks, the patient received 500,000 units of penicillin a day. This resulted, as before, in the suppression of symptoms, although the daily average temperature mounted progressively near the end of the course of treatment. A blood culture was positive for organisms the day after penicillin therapy was discontinued. The patient was in his fifth clinical relapse. Penicillin administration was resumed in higher dosage (1,200,000 units daily) on May 1, 1947. It was increased to 2,000,000 units daily on June 25 and maintained at that level until July 19, or for 24 days, when it was reduced to 1,200,000 units. Because of the patient's rising temperature in mid-August, the amount of penicillin was increased to 5,000,000 units a day for one week. After discontinuance of treatment with penicillin, the temperature elevation became more extreme and a blood culture yielding organisms was again obtained. Therapy with 1,200,000 units of penicillin daily was accordingly resumed, and streptomycin, 3.0 Gm. daily, was given concurrently from September 16 through 26. Soon thereafter, on September 29, the patient suffered a cerebral embolism, with resultant left-sided hemiparesis; otherwise his condition was in clinical remission for approximately three weeks following this brief period of combined therapy (fig. 2).

The patient was hospitalized in the United States in November 1947, suffering the seventh relapse of his protracted illness. At that time, the strain of nonhemolytic Streptococcus isolated from the blood stream was inhibited in vitro by 0.10 unit of penicillin per cubic centimeter. As a subject in a clinical study[2] he received 14,000,000 units of penicillin daily by intravenous and intramuscular injection for a 10 day period (fig. 2). Defervescence was prompt, but clinical and

2. King, F. H.; Schneirson, S. S.; Sussman, M. L.; Janowitz, H. D., and Stollerman, G. H.: Prolonged Moderate Dose Therapy Versus Intensive Short Term Therapy with Penicillin and Caronamide in Subacute Bacterial Endocarditis [case 4], J. Mt. Sinai Hosp. **16**:35, 1949.

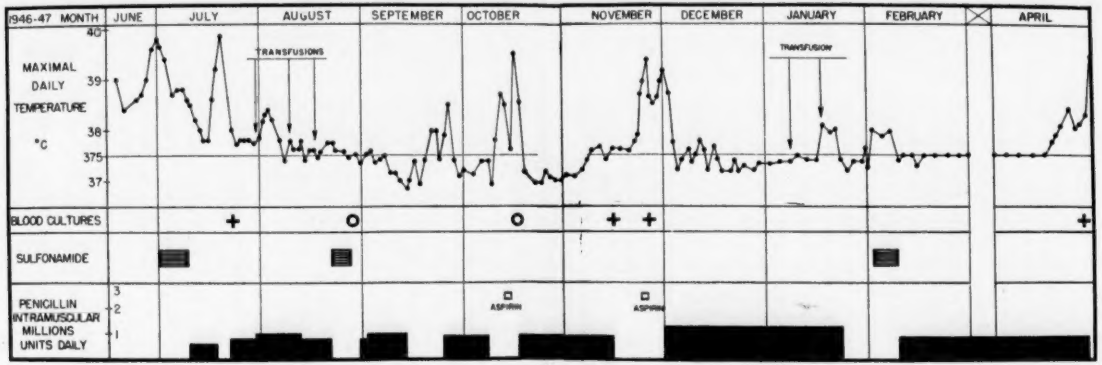


Fig. 1.—Course of illness of patient E. B., from first hospitalization elsewhere (June 1946) through April 1947.

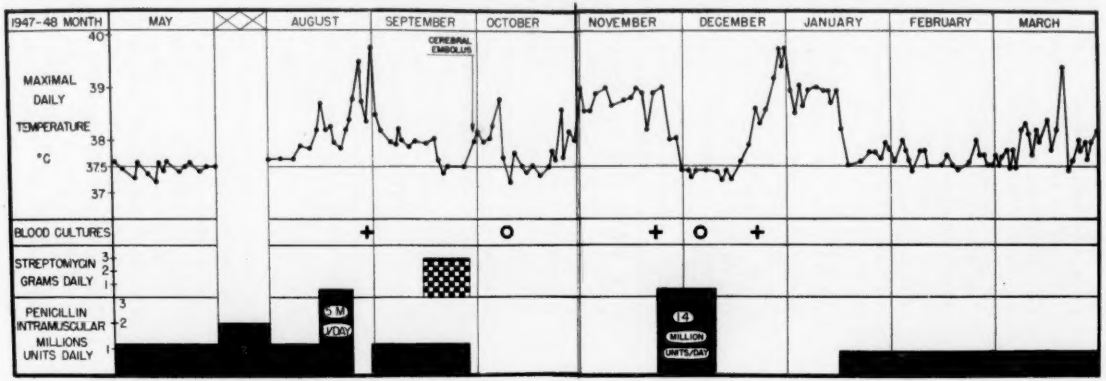


Fig. 2.—Course of patient's illness from May 1947 through March 1948.

bacteriologic relapse occurred within 14 days following therapy. The patient returned home, taking 300,000 units of procaine penicillin three times a day. On this regimen he was essentially free of symptoms, although mild malaise and daily afternoon fever (temperature of 38 C.) persisted (fig. 3). He maintained himself on this suppressive therapy throughout the entire year of 1948, the penicillin being administered to him by his wife.

The patient was admitted to the New York Hospital on Jan. 11, 1949. He had received up to that time a total of 825,000,000 units of penicillin and had sustained a total of eight relapses. Penicillin administration had invariably promptly suppressed fever and severe symptoms, but relapse had always been equally prompt after its withdrawal. Penicillin treatment was stopped the day before the patient was admitted to the hospital, and he promptly entered his ninth relapse (fig. 4).

On physical examination the patient was seen to be a well developed man who appeared mildly chronically ill. The rectal temperature was 38.5 C. (101.3 F.), the pulse rate 96 per minute, respiratory rate 20 per minute and the blood pressure 130/80 mm. Hg. The patient's weight was 71 Kg. The skin and mucosae were

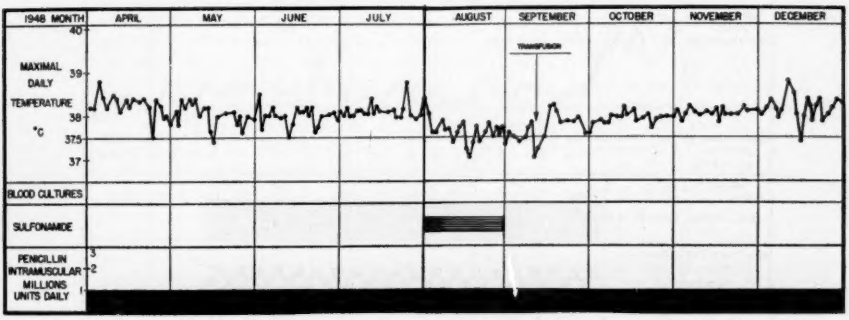


Fig. 3.—Course of patient's illness from April 1948 through December 1948.

slightly pale, and there were several petechiae scattered over the trunk and extremities. A petechia was present in the left palpebral conjunctiva, and one was on the inferior surface of the tongue. There were two recent flame-shaped hemorrhages in the right optic fundus. Examination of the heart revealed the point of maximal impulse to lie in the fifth interspace, 11 cm. from the midsternal line. The heart was in normal sinus rhythm. There was a long, rough, systolic murmur which was heard over the entire precordium, maximally at the apex. It was also easily heard in the axilla, but not over the base or neck vessels. There was no accentuation of the first sound at the apex, nor were any diastolic or presystolic murmurs audible. There were no thrills. The tip of the spleen was easily felt on inspiration. There were minimal signs of a residual left hemiparesis.

The blood contained a hemoglobin concentration of 11.5 Gm. per 100 ml.; there were 4,600,000 erythrocytes and 11,200 leukocytes per cubic millimeter. There were 60 mature polymorphonuclear leukocytes, 12 band forms, 22 lymphocytes, 14 monocytes, 1 eosinophil and 1 basophil per 100 leukocytes in the capillary blood. The hematocrit was 34 per cent, and the sedimentation rate (Wintrobe) was 45 mm. per hour. The urine contained albumin (3+); the sediment contained 2 to 4 erythrocytes and 2 to 4 leukocytes per high power field. The blood urea nitrogen

concentration was 11 mg. per 100 ml.; the serum albumin was 4.4 and the serum globulin 3.1 Gm. per 100 ml. The electrocardiogram showed left axis deviation. Roentgenographic examination of the chest revealed no abnormalities.

Five blood cultures obtained during the first week of hospitalization were all positive for a nonhemolytic Streptococcus, 5 to 15 colonies per milliliter. This organism was of a strain of nonhemolytic Streptococcus which produced alpha-hemolysis on horse and rabbit blood agar but did not produce a soluble hemolysin. Growth occurred at 10 C. (50 F.) but not following exposure to 60 C. (140 F.) for 30 minutes. Growth did not occur in 6.5 per cent sodium chloride broth. Gelatin was not liquefied, and mannitol was not fermented. The organism produced a large amount of dextran but no levan.[3] In vitro sensitivity tests showed the following concentrations of antibacterial substances to be inhibitory: penicillin 0.16 unit, streptomycin 125 micrograms and aureomycin 0.2 microgram, per cubic centimeter.[4]

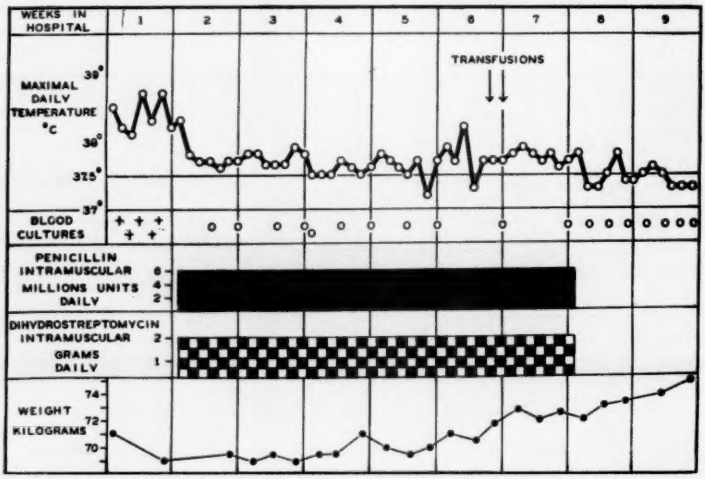


Fig. 4.—Patient's course during treatment at the New York Hospital from Jan. 11 to March 15, 1949.

The impression prior to treatment at the New York Hospital was that the patient had preexisting heart disease of undetermined type, probably rheumatic mitral valvulitis or a congenital septal defect, and chronically recurrent streptococcic endocarditis in relapse. Accordingly, combined therapy was started on the eighth hospital day (fig. 4). The patient received 500,000 units of crystalline sodium penicillin G every two hours intramuscularly and 0.5 Gm. of dihydrostreptomycin every six hours intramuscularly. Combined therapy was continued for a total of 42 days. Defervescence and reversal of bacteremia were prompt. The patient gradually felt stronger, exhibited more energy and an improved appetite and

3. This determination was made through the courtesy of Dr. Edward Hehre, Department of Bacteriology, Cornell University Medical College.

4. These tests were performed by the serial twofold dilution tube method.

steadily gained weight after the third week of therapy. The urine became clear except for a trace of albumin. Several carious teeth were removed and two blood transfusions were given during the period of therapy. Blood cultures remained sterile during a two week observation period following the discontinuance of penicillin and dihydrostreptomycin therapy. There were no symptoms or signs attributable to drug toxicity at any time.

The patient was discharged from the hospital on March 15, 1949. He has been seen in the follow-up clinic at regular intervals since his discharge; he has felt quite well, and all blood cultures have been sterile. On May 24, 1950 the patient was well and had traveled to Switzerland and returned without difficulty. His weight was 87.5 Kg. (a gain of 18.5 Kg. over his weight prior to combined therapy). There have been no symptoms of recurrence during the 14 months since completion of therapy. The patient's infection is believed arrested.

## COMMENT

It has been the general experience in the treatment of subacute streptococcic endocarditis that in approximately 15 per cent of all cases arrest of the infection is difficult to achieve with penicillin treatment. One portion of these cases is caused by enterococci, organisms uniformly resistant to penicillin. The remainder is caused by nonhemolytic streptococci, most frequently members of the Streptococcus viridans group, organisms not highly resistant to penicillin as customarily tested in vitro. The latter cases are, nevertheless, extremely refractory to penicillin treatment in that suppression of the signs of infection are readily obtainable with administration of penicillin, but relapses occur when it is discontinued.

In the case reported here failure to effect a sustained remission of the disease with penicillin treatment cannot be ascribed to a high degree of drug resistance of the causative organism. Taxonomically, the infecting organism is a member of the dextran-producing group of nonhemolytic streptococci described by Hehre and Neill [5] and termed Streptococcus s.b.e. (Streptococcus sanguis) by Loewe and his associates.[6] This subgroup has been found to be the causative agent in 40 per cent of all streptococcic (including enterococcic) endocarditis.[7] It has been implicated as the infecting organism in some cases of subacute streptococcic endocarditis which recurred following the usual penicillin therapy.[8]

That the nature of the parasite was responsible for the extreme refractoriness to penicillin which patient E. B. displayed is conceivable. It is equally probable, however, that the nature of the lesion, or a defect in the particular host's defense mechanisms, was the factor responsible for the failure of usually adequate penicillin therapy in this case.

The fact that the patient's infection was arrested after combined therapy with penicillin and dihydrostreptomycin suggests the potential value of this form of therapy in similar cases of chronic recurrent streptococcic endocarditis. The mechanism of the increased effectiveness of the antimicrobial combination has not been clarified. There is some evidence to support the hypothesis that the important

5. Hehre, E. J., and Neill, J. M.: Formation of Serologically Reactive Dextrans by Streptococci from Subacute Bacterial Endocarditis, J. Brit. Exper. Med. **83**:147, 1946.

6. Loewe, L.; Plummer, N.; Niven, C. F., Jr., and Sherman, J. M.: Streptococcus s.b.e. in Subacute Bacterial Endocarditis, J.A.M.A. **130**:257 (Feb. 2) 1946.

7. Hehre and Neill.[5] Loewe and others.[6]

8. Loewe, L., and Alture-Werber, E.: The Clinical Manifestation of Subacute Bacterial Endocarditis Caused by Streptococcus S.B.E., Am. J. Med. **1**:353, 1946.

underlying phenomenon is the elimination by streptomycin of organisms which, though prevented from multiplying, remain viable throughout exposure to high concentrations of penicillin.[9] According to this hypothesis, the elimination by the second drug (in this case streptomycin) of the bacteria which are suppressed by penicillin, but which are still viable, results in a reduction in the bacterial population to zero, or to a level sufficiently low that the host can eliminate them and relapse does not occur.

SUMMARY

A report is presented of the successful use of combined therapy with penicillin and dihydrostreptomycin in a case of nonhemolytic streptococcic endocarditis which had proved unusually refractory to prolonged and repeated penicillin therapy. Multiple relapses, nine in all, had occurred over a 2½ year period, despite the almost constant administration of penicillin, and despite the fact that the infecting organisms were not highly resistant to penicillin in vitro. Subsequent to treatment by the concurrent administration of penicillin and dihydrostreptomycin, the patient has been well and free from all signs of infection throughout a follow-up period of 14 months.

9. Robbins and Tompsett.[1] Spicer, S., and Blitz, D.: A Study of the Response of Bacterial Populations to the Action of Penicillin: A Quantitative Determination of Its Effect on the Organism, J. Lab. & Clin. Med. **33**:417, 1948.

# BACILLUS SUBTILIS MENINGITIS AND BACTEREMIA

## Report of a Case and Review of the Literature on "Subtilis" Infections in Man

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"Nonpathogenic" bacteria may occasionally cause serious or even fatal disease in man. Many instances of infection by such organisms have been reported; in a large number of cases they have been superimposed on a preexisting pathologic process, making evaluation of the role of the secondary invaders difficult. Frequently, even when they have appeared to be the primary inciting cause of an illness, conclusive evidence of the role of these "nonvirulent" bacteria has been lacking.

Among the "nonpathogenic" micro-organisms associated with human infection, various members of the Bacillus subtilis group have been noted uncommonly. This genus comprises the many aerobic, gram-positive, sporulating rods which are classified as Bacillus and includes Bacillus anthracis. Few laboratories attempt to distinguish the different species, with the exception of the anthrax bacillus, referring to them all as B. subtilis. More critical differentiation is made difficult not only by the inadequate descriptions of several of the named types, the many variants and the large number of unclassified organisms but also by the failure of bacteriologists to agree completely on the characteristics of the type species itself.[1] The problem, fortunately, is of academic interest only, since such exact classification appears to be of little or no clinical significance. It is the purpose of this paper to present a critical review of the available literature on human infection by B. subtilis and to add a case of meningitis in which the causative role of a member of this group was conclusively established. The term B. subtilis is used in this report in its generic sense.

Infection of the eye by various members of the subtilis group has been recognized quite frequently. This has been recorded oftenest after ocular trauma, such as presence of a foreign body, penetrating injury of the globe or, on occasion, surgical procedures. No attempt to review the literature on this subject is made in this paper. This has already been done by François [2] who, describing his observations in a case of severe conjunctivitis due to a foreign body, was able to

From the Haynes Memorial and Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston.

1. Soule, M. H.: Microbic Dissociation: I. B. Subtilis, J. Infect. Dis. **42**: 93-149, 1928; Identity of Bacillus Subtilis, Cohn 1872, ibid. **51**:191-215, 1932. Topley, W. W. C., and Wilson, G. S.: Topley and Wilson's Principles of Bacteriology and Immunity, ed. 3, revised by G. S. Wilson and A. A. Miles, Baltimore, Williams & Wilkins Company, 1946, pp. 848-855.

2. François, J.: Le bacille subtilique en pathologie oculaire, Bull. et mém. Soc. franç. d'ophth. **47**:423-437, 1934.

collect reports of 2 cases of dacryocystitis, 100 of conjunctivitis, 9 of keratitis, 4 of iridocyclitis, 41 of panophthalmitis and 1 instance of orbital abscess due to B. subtilis.

Four cases in which B. subtilis infection presented its most important manifestations in the lungs have been recorded. A patient with a fatal pulmonary infection with hemoptysis and hemorrhagic pleural effusion has been described by Wilamowski.[3] Cultures of the pleural fluid before death and of the effusion, spleen and bone marrow at autopsy yielded motile, gram-positive, sporulating bacilli which resembled B. anthracis except for their motility. No mention was made of the purity of the cultures. The bacilli proved pathogenic for animals on intraperitoneal inoculation; they were classified as belonging to the species pseudoanthracis. Keleman [4] reported an instance of pulmonary embolism following an operation for an incarcerated hernia in which, at autopsy, septic thrombi were observed in the veins around the operative site and in the left pulmonary artery. There were abscesses in the left lung and a purulent pleural effusion on the same side. A motile, gram-positive sporulating rod was isolated from the thrombi, the lung and the fluid in the pleural sac. The bacillus was identified as B. subtilis. A case of gangrene of the lung in which two antemortem blood cultures yielded B. subtilis has been noted by Bais.[5] Cultures of the pulmonary abscesses at necropsy were negative for these bacilli, however, although several other unspecified organisms were present; the spleen was sterile. These observations make it difficult to establish any relationship between the bacteremia and the pulmonary disease. Verdina [6] reported a case of abscess of the lung with recovery following treatment with antiseptics. From the sputum, which was purulent and blood tinged, large numbers of gram-positive motile bacilli resembling B. subtilis were cultivated. Reactions to skin tests with this organism, at first equivocal, became weakly positive in the later stages of the illness. On the sixtieth day, the patient's serum had an agglutinin titer of 1:380 and complement fixation reactions were positive.

Infection of the genitourinary tract with B. subtilis has also been described. In a case of unilateral pyelonephritis studied by Bonino,[7] an organism, identified as a member of the subtilis-mycoides group, was isolated from the urine and from the left ureteral orifice. It was pathogenic for animals, and the histopathologic changes in animals that died of the infection were thought to be particularly intense in the kidneys. Agglutination of the bacilli by the patient's serum was positive in a titer of 1:400. Hull, Howie and Bean [8] observed a schizophrenic patient with an initial infection involving the entire urinary tract and terminal spread to the meninges. At autopsy, multiple infarcts of the kidneys, pyelonephritis, cystitis, prostatitis and meningitis were observed, and a gram-positive, sporulating bacillus resembling

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3. Wilamowski, B. I.: Ueber einen Fall von Pseudoanthrax, Centralbl. f. Bakteriol. (Abt. 1) **66**:39-43, 1912.

4. Keleman, E.: Bacillus subtilis okozta sepsis es pneumonia: Vizsgalatok a bacillus subtilis korokozo voltarol. Gyogyaszat **64**:512-515; 531-533, 1924.

5. Bais, W. J.: A Case of Pathogenicity of Bacillus Subtilis, J. Infect. Dis. **40**:313-315, 1927.

6. Verdina, C.: Su di un caso di broncho-polmonite determinata da "Bacillus subtilis mycoides," Gior. di batteriol. e immunol. **3**:309-323, 1928.

7. Bonino, M.: "Il Bacillus subtilis mycoides" quale agente di pielonefrite grave con abolita funzionalità renale, Gior. di batteriol. e immunol. **13**:547-565, 1934.

8. Hull, E. R.; Howie, J. E., and Bean, H.: An Uncommon Infection of the Urinary Tract with Terminal Septicemia, Lancet **2**:189-190, 1937.

B. subtilis was isolated from all the lesions. The presence or absence of motility was not mentioned. An organism identified as B. subtilis was isolated in pure culture by Shultz [9] from a patient with multiple renal abscesses and "chronic and acute diffuse nephritis." Pellegrini [10] described a case of puerperal sepsis associated with a large uterine laceration which, at autopsy, revealed pyoendometrium, peritonitis and many small abscesses in the renal cortices and medullas. A culture of the blood yielded B. subtilis. Microscopic examination of the uterus showed degeneration of the muscle fibers and infiltration of the muscular layers by neutrophils and great numbers of large, long bacilli, while the kidneys revealed tubular degeneration and perivascular collections of bacteria resembling those seen in the myometrium. Two instances of infection presumed to be due to members of the subtilis group have been reported by Trivellini.[11] In one case, prolonged puerperal sepsis was followed by the development of a large abscess in the right lower portion of the abdominal cavity. Death occurred after a period of months; autopsy revealed that amyloidosis was a contributing cause. Culture of pus aspirated from the abscess prior to death yielded Bacillus mycoides, which was agglutinated by the patient's serum in a dilution of 1:350. Injection of these organisms into rats and rabbits produced death. The second patient was a man who four years previously had had a pustule on the glans penis which progressed to produce ulceration, pronounced penile swelling and multiple urethral fistulas. Serologic tests for syphilis gave negative reactions. A culture of exudate from the lesion revealed an organism intermediate in its characteristics between B. subtilis and B. mycoides. Cure followed surgical removal of the affected area of the penis. It appears doubtful that the bacillus isolated in this case was the primary cause of the disease; it is likely that it was acting only as a secondary invader.

B. subtilis has been suspected as a cause of food poisoning by two investigators. Lubenau [12] observed an outbreak of food-borne gastroenteritis in a psychiatric hospital. No pathogenic bacteria were isolated from the stools of the patients. An organism resembling B. subtilis, but differing from it in some biochemical characteristics, was isolated from the suspected food, however. Feeding of whole cultures of this bacillus to dogs produced diarrhea, but filtrates caused no demonstrable illness; the bacteria could not be recovered from the feces of the experimental animals. Subcutaneous inoculation into mice and guinea pigs was without effect. A fatal case of severe, acute enteritis in a young Chinese, from whose feces a pure culture of bacteria resembling B. anthracis was obtained, has been recorded by Seitz.[13] The organism did not possess the biochemical activities of B. subtilis, was motile and was highly pathogenic for mice. Subcutaneous injection of living or killed cultures caused death in experimental animals in three days, while feeding also was lethal, the organisms being recoverable from the feces. The administration of sterile culture filtrates subcutaneously killed guinea pigs.

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9. Shultz, W. G.: Bacillus Subtilis Infection of the Kidney, Urol. & Cutan. Rev. **42**:493-498, 1938.

10. Pellegrini, F.: Contribution à l'étude de la microbiologie du "B. subtilis": Le "B. subtilis" comme cause de septicémie et de mort, Soc. Internaz. di microbiol., Boll. d. sez. ital. **6**:492-500, 1934.

11. Trivellini, A.: Infezioni da Bacillus subtilis-mycoides, Boll. e mem. Soc. piemontese di chir. **2**:1608-1623, 1932.

12. Lubenau: Bacillus peptonificans als Erreger einer Gastroenteritis-Epidemie, Centralbl. f. Bakteriol. **401**:433-437, 1905-1906.

13. Seitz, A.: Pathogener Bacillus subtilis, Centralbl. f. Bakteriol. (Abt. 1) **70**:113-114, 1913.

Members of the subtilis group have been incriminated as the cause of meningitis four times prior to the present report. Meningeal infection due to an anthracoid bacillus of undetermined species following spinal anesthesia has been described by Senge.[14] Direct examination of the spinal fluid showed both extracellular and intracellular bacilli. These were only questionably motile, but differentiation from B. anthracis was made on the basis of the pathologic picture, the relatively low degree of pathogenicity for animals and a negative Ascoli reaction. Lindberg[15] reported an instance of intracranial hemorrhage followed one and a half months later by a subdural abscess in the right cranial hemisphere in a young infant. After surgical evacuation of the local lesion, there was spread of the infection to the lateral ventricle and the base of the brain. Cultures, as well as direct smears, of the material obtained at operation revealed B. subtilis; the same organism was observed in the heart blood at autopsy two hours after death. In a case of mastoiditis due to chronic otitis media in a 25 year old man, Sanderson[16] reported complete necrosis of the bone, exposure and inflammation of the meninges and a pure culture of B. subtilis in the mastoid at the time of operation. The patient's condition became progressively worse postoperatively, and the clinical picture of meningitis developed. The spinal fluid was not examined, so that no bacteriologic relationship between the disease in the meninges and that in the mastoid could be established. A fatal instance of meningitis due to an anthracoid bacillus resembling Bacillus megatherium has been noted by Bruynoghe and Ronse.[17] The organism was virulent for mice when given either intraperitoneally or subcutaneously.

Local suppurative lesions for which B. subtilis was thought to be responsible have been reported three times. An "unusual form of abscess" from which was isolated an organism that resembled B. anthracis, except for lack of pathogenicity for animals, was described by McFarland.[18] A definite relationship between the bacillus and the lesion could not be established. Mela[19] isolated an organism with some of the characteristics of both B. subtilis and B. mycoides from the exudate in a patient with a perimandibular abscess arising from an infected tooth. The bacillus was nonpathogenic for rabbits and guinea pigs but virulent for mice. A case of suppurative lymphadenitis involving the right axillary and lateral cervical nodes followed by generalized infection and bacteremia due to B. subtilis has been described by Cardia.[20] Incision of the suppurating areas was followed by chronic drainage of exudate and considerable scarring. Treatment with heavy metals and iodides produced no response, and death occurred as a result of bronchopneumonia. The organism was virulent for rabbits and was agglutinated by a 1:500 dilution of the patient's serum.

14. Senge, J.: Meningitis purulenta et Encephalitis haemorrhagica nach Lumbanästhesie, verursacht durch einen eigenartigen Sporenbildner, Centralbl. f. Bakteriol. (Abt. 1) **70**:353-368, 1913.

15. Lindberg, G.: Meningeal Hæmorrhage with Infection by B. Subtilis in an Infant, Hygiea **78**:1089-1112, 1916.

16. Sanderson, D. D.: Bacillus Subtilis in Pure Culture Complicating Mastoiditis and Meningitis, Nebraska State M. J. **11**:318, 1926.

17. Bruynoghe, R., and Ronse, M.: Une infection méningée par un bacille anthracoide, Compt. rend. Soc. de biol. **125**:395-397, 1937.

18. McFarland, J.: Bacillus anthracis similis, Centralbl. f. Bakteriol. (Abt. 1) **24**:556-557, 1898.

19. Mela, B.: Su di un caso di osteoflemmone perimandibolare odontogeno da "Bacillus subtilis-mycoides," Gior. di batteriol. e immunol. **8**:350-352, 1932.

20. Cardia, A.: Contributo alla conoscenza delle infezioni da Bacillus subtilis, Arch. per le sc. med. **60**:59-68, 1935.

The presence of B. subtilis in association with disease processes initiated by other micro-organisms has also been described. Kruse and Pasquale [21] reported the isolation, at autopsy, of B. subtilis from the portal vein and liver of a patient with amebic dysentery and multiple hepatic abscesses. Material aspirated from one of the hepatic lesions shortly prior to death, however, was sterile. It seems unlikely that the recovery of B. subtilis at necropsy was more than incidental, representing agonal or postmortem invasion or possibly contamination at the time of aspiration. A strain of B. subtilis pathogenic for rats, together with a variety of other organisms, was reported by Sweany and Pinner [22] in the pleural, pericardial and peritoneal fluids and heart blood of a patient with acute and chronic disseminated tuberculosis; also isolated were nonhemolytic streptococci, pneumococci and Staphylococcus pyogenes var. aureus and Escherichia coli. Bory [23] recovered B. subtilis on two of three occasions from the buboes of a patient with proved lymphogranuloma venereum. A fatal instance of membranous tonsillopharyngitis with B. subtilis bacteremia was noted by Anghelesco and Fasie.[24] The culture of a cervical lymph node, the tonsils and lungs revealed predominantly "streptococci," rare thick gram-negative bacilli and gram-positive sporulating rods. It seems probable, therefore, that the presence of the subtilis bacilli, which were shown to be nonpathogenic for animals, represented only secondary invasion facilitated by the breaking down of defense mechanisms by an overwhelming streptococcic infection.

The most recent report of a case of infection with B. subtilis is that of Yow, Reinhart and Butler.[25] They studied a 12 week old infant with the clinical and laboratory picture of acidosis and pyelonephritis who, one week before, had been given a blood transfusion because of anemia. B. subtilis was present in the urine and blood on the day of hospitalization; blood cultures yielded the organism on five subsequent occasions through the twelfth day in the hospital. Therapy consisted of sulfadiazine for an unspecified period, penicillin for twenty-one days and sixth-molar lactate solution, administration of which was continued by the oral route until the child was 14 months old. The bacteremia was thought to have been initiated by transfusion of contaminated blood and the renal infection to represent a metastatic bacterial lesion.

### REPORT OF CASE

D. B., a 26 year old white man, was sent to the Haynes Memorial Hospital, with a diagnosis of meningitis, probably due to B. subtilis. Two days prior to his admission, pain developed in the right lower abdominal quadrant and a diagnosis of appendicitis was made. On his entry to another hospital, the temperature was 100.2 F., the pulse rate 100 and respirations 20. The white blood cell count was 12,000; the urine was normal. An appendix which was swollen and reddened at the tip was removed at operation, with the patient under spinal anesthesia induced with procaine hydrochloride in dextrose solution. The cerebrospinal fluid withdrawn

21. Kruse, W., and Pasquale, A.: Untersuchungen über Dysenterie und Leberabscess, Ztschr. f. Hyg. u. Infectionskrankh. **16**:1-148, 1894.

22. Sweany, H. C., and Pinner, M.: A Pathogenic Subtilis Bacillus from a Patient with Chronic Tuberculosis, J. Infect. Dis. **37**:340-343, 1925.

23. Bory, L.: Sur l'étiologie de la maladie de Nicolas-Favre: Du rôle pathogène possible d'une variéte de "B. subtilis" dans cette affection, Bull. Soc. franç. de dermat. et syph. **35**:2-5, 1928.

24. Anghelesco, V., and Fasie, S.: A propos des infections à Bacillus subtilis, Revista stünt. med. **26**:183-190, 1937.

25. Yow, M. D.; Reinhart, J. B., and Butler, L. J.: Bacillus Subtilis Septicemia Treated with Penicillin, J. Pediat. **35**:237-239, 1949.

before the introduction of the anesthetic solution was slightly blood tinged. The following afternoon, fever and pain developed in the legs and he became unresponsive, thrashed about and, in about eight hours after the first onset of symptoms, was comatose, exhibited athetosis, purposeless ocular movements, sluggishly reacting pupils, generalized areflexia, the presence of Kernig's signs and stiffness of the neck. The white blood cell count was 35,000, and lumbar puncture revealed turbid, pink-tinged fluid which was "loaded with polymorphonuclear leukocytes" and contained a moderate number of red blood cells. Five grams of sodium sulfadiazine was given intravenously in saline solution. The clinical condition was unimproved the following day, when cultures of the spinal fluid grew B. subtilis and rare colonies of hemolytic Staph. pyogenes var. aureus. Another spinal tap showed the fluid to be less turbid but still slightly blood tinged; a gram-stained smear was examined by one of us (L. W.) and observed to contain gram-positive bacilli in various stages of phagocytosis. The patient was then transferred to the Haynes Memorial Hospital.

Physical examination on his admission to this hospital revealed a well developed, well nourished, comatose young man, making purposeless motions of the arms and mouth and resisting examination. The temperature was 102.2 F. (rectum), the pulse rate 92 and respirations 20 per minute. The eyes moved aimlessly about; the pupils did not respond to light, and there was mild conjunctival injection. The mucous membranes of the mouth and pharynx were dry. The neck and back were stiff. The lungs were clear. The heart was normal in size, and there was a harsh apical systolic murmur transmitted toward the axilla. The abdomen revealed a clean appendectomy incision. The genitalia and extremities were not remarkable. Except for an equivocal plantar response on the right, no superficial or deep tendon reflexes could be elicited. Kernig's sign was present. A catheterized urine specimen showed a 2 plus reaction for albumin, 4 to 6 leukocytes, 1 to 3 erythrocytes and a few granular casts per high power field. There was no anemia. The white blood cell count was 12,450, with 84 per cent neutrophils, 12 per cent lymphocytes and 4 per cent eosinophils. Lumbar puncture revealed an initial pressure of 310 mm., and a poor response to jugular compression. The fluid had a "ground-glass" appearance and contained 115 mg. of sugar, 39 mg. of protein and 702 mg. of chloride per hundred cubic centimeters; the cell count was 23,250, of which 18,750 were white blood cells (95 per cent neutrophils, 5 per cent lymphocytes) and the remainder erythrocytes. Stained smears showed both intracellular and extracellular gram-positive rods. Spinal fluid and blood cultures yielded a pure growth of B. subtilis.

Treatment on his admission consisted of 1 Gm. of sulfadiazine every four hours, sedation and hydration with fluids given intravenously. The following day the patient responded slowly to questions and commands, and the spinal fluid showed a reduction in the number of white blood cells to 2,040, with 60 per cent polymorphonuclear leukocytes; the protein content was 250 mg. per hundred cubic centimeters, and the sugar level was normal. The blood culture was negative after two days but the organisms were present in the cerebrospinal fluid for the first four days. On recovering consciousness (second day), the patient had severe weakness of both legs and was unable to void spontaneously. On the fourth hospital day he complained of numbness in the legs and in the first three fingers of the left hand. During the ensuing six weeks there was steady improvement; headache, the most distressing symptom, gradually disappeared, and there was progressive return of strength to the lower extremities. Chemotherapy was discontinued after fourteen days. Inability to void, which was present on his admission, persisted until the thirty-fifth day in the hospital; a considerable urine residual was still present for about a week after the start of spontaneous micturition. At the end of one month the spinal fluid was

essentially normal except for an elevated protein content and sluggish response to jugular compression. The patient was sent home on the forty-ninth hospital day.

Six months later he returned to the hospital complaining of increasing weakness and loss of sensation in the legs of three weeks' duration. After his discharge from the hospital, his condition had continued to improve and he had gone back to work. The only complaints during this period were severe constipation, slight generalized weakness and numbness over the buttocks and the posterior aspects of both thighs. About three weeks prior to readmission, weakness of both legs, which gradually became more pronounced on the left, was noted. He stumbled and tripped frequently and had great difficulty getting about; there were also complete loss of sensation in the right leg and diminished sensation in the left leg. Results of physical examination were not remarkable except for the neurologic findings. The biceps jerk, radial periosteal reflex and knee jerk were hypoactive; the triceps and ankle jerks were absent, as were the lower abdominal and cremasteric reflexes; the Babinski and Hoffmann signs were not present. The finger to nose test showed normal coordination, but there was difficulty with ataxia of the right lower extremity. The Romberg sign was present. The left leg showed decided weakness and a slight foot drop. Position sense was intact. Reaction to light touch was decreased on the second to fifth toes and the lateral aspects of both feet. Pinprick sensation was diminished over the entire right leg and the anterolateral aspect of the thigh and the posterior aspect of the lower part of the leg on the left. Temperature sensation was absent on the anterior aspect of the lower leg and the dorsum of the foot and was diminished over the entire posterior portion of the leg, except for the plantar surface of the foot on the right. The urine was not remarkable. There was no anemia or leukocytosis. Lumbar puncture revealed normal pressure and a sluggish response to jugular compression. The spinal fluid was xanthochromic and contained 70 mg. of sugar, 92 mg. of protein and 656 mg. of chloride per hundred cubic centimeters. The colloidal gold reaction was negative. There were 1,115 cells, all erythrocytes, per cubic millimeter; no organisms were seen on smear and cultures were negative.

Because of the possibility that the patient's difficulties might be on the basis of an epidural abscess, he was given full doses of sulfadiazine again. On this regimen some return of strength to the legs and a decrease in the extent of the sensory involvement occurred. Lumbar puncture repeated on the seventh day in the hospital gave the following findings: Pressure was unobtainable, and there was no response to jugular compression; the fluid was yellow. The protein had risen to 1,200 mg. per hundred cubic centimeters; all the other studies gave normal results except for the presence of 3,970 red blood cells per cubic millimeter.

On the eleventh hospital day the patient was transferred to the neurosurgical service of another hospital. There, a subarachnoid cyst at the level of the eighth and ninth thoracic vertebrae was removed. There was improvement for a short time following operation, but subsequently pain in the lower part of the back developed radiating anteriorly to both sides and down the posterior aspect of the left leg; it was aggravated by coughing, sneezing or straining at stool. Readmission after three months revealed hypesthesia from the waist down, most prominent in the perianal and postscrotal areas, weakness of the muscles of both legs particularly on the left, absence of both ankle, the right knee and left cremasteric reflexes and marked presence of the Romberg sign. The old operative site was reopened, and adhesions between the cord and the dura both above and below the area where the cyst had been were freed. Following operation, there were again return of strength and sensory function and reversion of the neurologic signs toward normal. One month later fever, headache, stiffness of the neck and the Kernig sign bilaterally made their appearance. No spinal fluid could be obtained. An aspetic meningitis caused by

reaction to the fibrin foam placed in the spinal canal at operation was considered as the most likely cause of these manifestations. Sulfadiazine, in full doses, was given, and complete recovery took place in two days. For approximately the next four and one half years the patient did well and carried out his business and some light sport activities. About six years after the first onset of the meningitis, he noted that he dragged his left foot on walking and stumbled going upstairs. Physical examination showed weakness of the left leg and ankle, hypesthesia of both lower extremities, more pronounced on the right, diminished reflexes in the right leg and conspicuous presence of the Romberg sign. Only a few drops of spinal fluid could be obtained on lumber puncture. Oxygen spinogram revealed air in the lumbar sac and a small amount under the tentorium. A diagnosis of spinal cord adhesions was made, but no further surgical procedures were carried out.

### BACTERIOLOGIC AND SEROLOGIC STUDIES

The organism isolated from the spinal fluid and blood of the patient described previously was studied in an attempt to classify it. Stained preparations of a twenty-four hour old broth culture showed stubby, fat, gram-positive rods with slightly rounded ends, growing singly or occasionally in short chains of two or three. Rare bacilli revealed central ovoid spores which did not cause bulging of the cell. There was a sluggish, twisting type of motility. Growth in broth produced uniform turbidity of the medium without formation of a surface scum. On plain agar, slightly irregular, light yellow, rounded, flat, rough colonies with a raised center, 1.5 to 3 mm. in diameter, and with slightly serrate edges were formed. On blood agar each colony was surrounded by a 1 mm. zone of hemolysis. Slow coagulation, peptonization and decolorization from above downward, without acid formation, were produced in litmus milk. Gelatin was liquefied slowly. Acid, without gas, was formed in glucose, maltose, levulose, dextrin and trehalose; sucrose, lactose, inulin, mannitol, dulcitol, sorbitol, glycogen and starch were not attacked. Intraperitoneal inoculation of 0.1 cc. of an eighteen hour broth culture into mice caused death in six hours; bacteria could not be recovered from the heart blood at autopsy. A 1:100 dilution of culture (0.1 cc.) injected by the same route and subcutaneous injection of 0.1 cc. of undiluted material produced no demonstrable disease. These observations do not allow the organism to be placed exactly in any of the recognized species belonging to the "subtilis" group; it has features which suggest a close relationship to Bacillus mesentericus (Bacillus pumilus).

Serologic studies were made in an attempt to demonstrate a causal relationship between the strain of bacteria isolated from the spinal fluid and blood. Specimens of the patient's serum were collected at weekly intervals for the first seven weeks of illness. Antigen was prepared by growing the organisms on heart infusion agar for eighteen hours, washing them off with phenolized isotonic sodium chloride solution, filtering through sterile cotton and adjusting the turbidity to a value of 3 on the McFarland nephelometer scale. The agglutinin titer of the patient's serum against his organisms was 1:2 on the third day of illness; by the end of the third week it had risen to a dilution of 1:1,024. At the time of his discharge from the hospital, seven weeks after the onset of the meningeal infection, the titer of serum agglutinin was still elevated to 1:256.

### COMMENT

Although the drugs used for this patient could not be examined bacteriologically, the likelihood is great that the meningitis resulted from the accidental introduction of organisms during the production of spinal anesthesia. It is impossible to state whether the bacteria were present in the solutions that were used or were resident

on the skin. This case represents, therefore, not a primary meningeal infection but rather a secondary one due to "trauma." This is usually the situation when meningitis is produced by essentially "nonpathogenic organisms." The general infrequency of meningitis in man following lumbar puncture in the presence of bacteremia and the absence of any evidence suggesting the presence of B. subtilis in the blood stream prior to operation militates against the possibility that the bloody spinal puncture may have initiated the meningitis. It is interesting to speculate, however, regarding the role of the small amount of blood in the cerebrospinal fluid, together with the dextrose added by the administration of the anesthetic, in enhancing the chance of survival and growth of the organisms by providing a more favorable medium. This does not seem likely.

The initial response to sulfadiazine, while not dramatic, was at least satisfactory. Bacteremia disappeared on the third day, and the spinal fluid became sterile after four days. In general, the members of this group of bacteria are not sensitive to the sulfonamides, showing a much greater sensitivity to penicillin, aureomycin, chloramphenicol and, in some cases, streptomycin. At the time this case was studied, penicillin was available only in limited quantities. It is possible that had this antibiotic been employed and more rapid elimination of the infecting organisms produced, the distressing sequelae might have been prevented in some degree. The use of sulfonamide drugs in this type of infection is not completely without experimental basis, however. Rosenthal [26] reported that sulfanilamide added to nutrient mediums does not cause cessation of growth but inhibits spore formation and induces degenerative changes in the vegetative forms of the subtilis group of bacteria.

The mere isolation of an organism in a case of infection does not always constitute conclusive evidence that it is the causative agent, particularly if other disease processes or other known pathogenic bacteria are present. This does not imply that the previously reported cases do not represent true instances of invasion by B. subtilis. It is important to emphasize, however, that when dealing with organisms of "low virulence" great care must be exercised in assigning significance to their presence. The demonstration of a single elevated agglutinating or complement fixating titer against bacteria recovered from some local focus or the blood does not constitute unequivocal evidence of a causal relationship; a level of antibody titer which rises during the course of a disease is of much greater value in firmly establishing a diagnosis. In the case presented here, the bacteriologic evidence was strongly suggestive that a strain of B. subtilis was the cause of the meningitis, even though a rare colony of hemolytic Staph. pyogenes var. aureus was found in the spinal fluid on initial examination; later cultures yielded only the gram-positive rod in both the blood and the cerebrospinal fluid. In addition, the same bacilli were seen on several occasions in stained smears of spinal fluid where they were found, most frequently, inside polymorphonuclear leukocytes. The demonstration of a rising titer of agglutinin against the isolated strain during the course of the patient's illness would appear to establish the role of the organism in the production of the meningitis and bacteremia.

Cases of this type probably occur with greater frequency than is reported in the literature. The "subtilis" group is well known to all bacteriologists as a common laboratory contaminant, and its presence is usually dismissed as fortuitous by both the technician and the physician. It is entirely possible that many cases of infection produced by these bacteria go unrecognized because of this easily understandable error. The demonstration of B. subtilis in a culture should not be dismissed com-

26. Rosenthal, L.: Action of Sulfanilamide in Vitro on Aerobic Sporogenic Bacilli, Proc. Soc. Exper. Biol. & Med. **43**:78-80, 1940.

pletely, particularly in atypical infections or when trauma is followed by bacterial invasion. The original culture of the spinal fluid of the patient presented here is a good example of an instance in which the "contaminant," B. subtilis, was the pathogen, while the "pathogen," hemolytic Staph. pyogenes var. aureus, was probably a contaminant, since it was demonstrated in only one culture of spinal fluid.

## CONCLUSIONS

A case of suppurative meningitis and bacteremia due to a member of the "subtilis" group closely related to Bacillus mesentericus (Bacillus pumilus) is presented. The meningeal infection was probably the result of accidental introduction of organisms during the process of producing spinal anesthesia. The acute phase of the meningitis responded rapidly to therapy with sulfadiazine.

The presence of members of the "subtilis" group in local infections or in the blood stream of man cannot always be considered the result of "contamination"; rarely, these essentially "nonvirulent" organisms may produce severe disease.

The literature on human infections with B. subtilis and related organisms is reviewed.

# Progress in Internal Medicine

## GASTROENTEROLOGY

**A Review of the Literature from July 1948 to July 1949**

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   - Tumors
   - Appendices Epiploicae
12. Colon
   - Proctoscopic Examination
   - Megacolon
   - Volvulus
   - Diverticulosis and Diverticulitis
   - Gas
   - Foreign Bodies
   - Irradiation Proctitis
   - Experimental Studies of Colonic Function in Man
   - Effect of Methacholine on Colon of Dogs
   - Ulcerative Colitis
   - Polyps and Other Tumors
   - Carcinoma
13. Anus and Rectum
   - Fecal Continence
   - Anal Spasm
   - Pruritus—Hemorrhoids
   - Tuberculosis

14. Miscellaneous Gastrointestinal Subjects
    Appetite
    Nutritional Problems
    Effect of Streptomycin on Fecal Flora
    Peritonitis
    Vascular Accidents
    Large Intestinal Colic Due to Sympathetic Deprivation
    Hernia

PEPTIC ULCER (CONTINUED)

*Surgical Treatment and Results.*—Subtotal gastrectomy continues to be the best surgical approach to the problem of treatment of peptic ulcer in the opinion of many authors.[212]

*Postgastrectomy Syndrome.*—The symptoms encountered in a group of 20 patients who, after partial gastrectomy for ulcer, presented difficult nutritional problems are divided into two groups: "early" and "late" postprandial symptoms.[213] The early symptoms of epigastric pressure, nausea and fulness, eructation and belching, dizziness and occasional vomiting are attributed to mechanical factors: distention and rapid emptying of the small stomach and overflooding of the small intestine. The late symptoms of headache, fatigue, palpitation, weakness, vertigo and occasional precordial pressure are ascribed to chemical factors: hypoglycemia secondary to the exaggerated postprandial hyperglycemia. Psychoneurotic factors are believed to contribute materially

212. St. John, F. B.; Harvey, K. D.; Ferrer, J. M., and Sengstaken, R. W.: Results Following Subtotal Gastrectomy for Duodenal and Gastric Ulcer, Ann. Surg. **128**:3, 1948. Gaviser, D.: Clinical Investigation and Evaluation of 416 Cases Consecutively Operated upon for Peptic Ulcer, Surgery **24**:873, 1948. Marshall, S. F.: Partial Gastric Resection for Peptic Ulcer, S. Clin. North America **29**:767, 1949. Garlock, J. H., and Lyons, A. S.: The Surgical Therapy of Duodenal Ulcer, Surgery **25**:352, 1949. Milstein, B. B.: Immediate Results of Partial Gastrectomy for Peptic Ulcer, Lancet **1**:514, 1949. Porter, H. W.: Partial Gastrectomy for Peptic Ulcer, Edinburgh M. J. **55**:549, 1948. Hosford, J.: Some Aspects of Partial Gastrectomy, Brit. M. J. **1**:929, 1949. Mimpriss, T. W., and Birt, St. J. M. C.: Results of Partial Gastrectomy for Peptic Ulcer, Brit. M. J. **2**:1095, 1948. Porter, H. W., and Claman, Z. B.: A Preliminary Report on the Advantages of a Small Stoma in Partial Gastrectomy for Ulcer, Ann. Surg. **129**:417, 1949. Crile, G. C., Jr.: The Surgical Treatment of Peptic Ulcer, S. Clin. North America **28**:1123, 1948. Welch, C. E., and Allen, A. W.: Gastric Ulcer—A Study of the Massachusetts General Hospital Cases During the Ten-Year Period 1938-1947, New England J. Med. **240**:277, 1949. Lozano Blesa, R.: Surgical Methods in the Treatment of the Gastroduodenal Ulcer, Rev. españ. enferm. ap. digest. y nutrición **7**:704, 1948. Griswold, R. A.: Rationale for Surgical Treatment of Duodenal Ulcer, Surg., Gynec. & Obst. **88**:585, 1949. Reccius, A.: La úlcera yuxtacardíaca y del tercio superior del estómago: Su tratamiento por el método Kelling-Madlener, Prensa méd. argent. **35**:2313, 1948. Spak, I.: "Palliative Gastrectomy" in Cases of Duodenal Ulcer, Acta chir. Scandinav. **97**:91, 1948-1949.

213. Adlersberg, D., and Hammerschlag, E.: Mechanism of the Postgastrectomy Syndrome, J. A. M. A. **139**:429 (Feb. 12) 1949.

to the symptomatology. Schechter and Necheles [214] think that the "hyperglycemic shock" theory is not valid; early postprandial symptoms probably bear no etiologic relation to the abnormal oral dextrose tolerance curves. In 24 cases the symptoms occurred while the patients were in the hyperglycemic stage.[215] Bulky meals, regardless of carbohydrate content, were more apt to produce symptoms. The syndrome is related to mechanical distention of the intestine and stimulation of the sympathetic nervous system. Duprez [216] recommends the use of atropine intravenously and vagus section in therapy. [In the experience of the reviewers, however, symptoms usually identified with the dumping syndrome also have been encountered after vagotomy.]

*Postgastrectomy Gastritis.*—Among 25 patients who had undergone gastric resection chiefly for duodenal ulcer and who returned because of persistent symptoms referable to the gastrointestinal tract, gastroscopy revealed a normal stomach in one patient; one patient had a lesion of indeterminate origin. Postoperative gastritis or gastrojejunitis of sufficient severity to account for the symptoms was observed in the remaining 23 patients.[217] Microscopic examination at the time of the original operation had disclosed coexistent gastritis in all members of the group.

*Ligation of Vessels.*—Ligation of the vessels to the stomach and gastroenterostomy proved ineffective in 47 patients with peptic ulcer; the tendency to stomal ulceration was no less than after gastroenterostomy alone.[218]

*Vagotomy—Anatomic and Physiologic Observations.*—In a study of 50 cadavers, Jackson [219] noted four types of vagal trunks. The physiologic aspects of vagotomy are discussed by various authors.[220] Emphasis

214. Schechter, S. E., and Necheles, H.: Postprandial Symptoms Following Subtotal Gastrectomy for Peptic Ulcer and Their Relationship to the Glucose Tolerance Curve, Gastroenterology **12**:258, 1949.

215. Irvine, W. T.: Post-Prandial Symptoms Following Partial Gastrectomy, Brit. M. J. **2**:514, 1948.

216. Duprez, A.: Contribution à l'étude des troubles du metabolisme glucidique survenant après gastrectomie subtotale, Ann. Soc. roy. sc. med. et nat. **1**:97, 1948.

217. Gray, H. K.; Meyers, W. C., and Dockerty, M. B.: Postgastrectomy Gastritis, S. Clin. North America **28**:965, 1948.

218. Wood, W. Q.: Treatment of Peptic Ulceration by Vascular Ligation, Arch. Surg. **58**:455 (April) 1949.

219. Jackson, R. G.: Anatomy of the Vagus Nerves in the Region of the Lower Esophagus and the Stomach, Anat. Rec. **103**:1, 1949; Anatomic Study of the Vagus Nerves, with a Technic of Transabdominal Selective Gastric Vagus Resection, Arch. Surg. **57**:333 (Sept.) 1948.

220. Griswold, J. A.: Physiologic Changes Following Vagotomy for Peptic Ulcer, South. Surgeon **15**:1, 1949. Thomas, J. E., and Komarov, S. A.: Physiological Aspects of Vagotomy, Gastroenterology **11**:413, 1948. Dragstedt, L. R.: The Question of Complete Vagotomy in Man and Experimental Animals, ibid.

is placed on the importance of repeated postoperative tests, since the response of the stomach within the first two weeks after operation is likely not to be representative of its true condition.

*Gastric Mucosa After Vagotomy.*—Twenty patients, 19 with duodenal ulcer and 1 with jejunal ulcer, were examined gastroscopically at intervals of three to twelve months after vagotomy alone or combined with either pyloroplasty or gastroenterostomy.[221] The impression is gained that vagotomy produces definite gastritic changes, although with less frequency when a gastroenterostomy opening is established concomitantly. It should be noted that some type of gastritis was described in 8 of the 11 patients examined by gastroscope before operation. [The reviewers have found that vagotomy does not alter the gastroscopic appearance of the gastric mucosa. Furthermore, the histologic appearance of the stomach at intervals of one week to four years eight months after vagotomy usually does not differ significantly from that often observed in ulcer patients with intact vagus nerves and in persons with no history of gastric disease.]

Gastroscopic studies were carried out in 24 patients with vagotomy alone, with gastroenterostomy and with subtotal gastric resection made during the first postoperative year.[222] In those with simple vagotomy the observations were gastric dilatation and atony, peristaltic inactivity and lack of mucosal change; the pylorus was patulous rather than contracted. In those with vagotomy and gastroenterostomy the mucosal

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**12**:1010, 1949. Hollander, F.: Laboratory Procedures in the Study of Vagotomy, ibid. **11**:419, 1948. Machella, T. E., and Lorber, S. H.: Gastrointestinal Motility Following Vagotomy and the Use of Urecholine for the Control of Certain Undesirable Phenomena, ibid. **11**:426, 1948. Postlethwait, R. W.; Hill, H. V., Jr.; Chittum, J. R., and Grimson, K. S.: Effect of Vagotomy and of Drugs on Gastric Motility, Ann. Surg. **128**:184, 1948. Stein, I. F., and Meyer, K. A.: Studies on Vagotomy in the Treatment of Peptic Ulcer: III. Physiological Aspect, Surg., Gynec. & Obst. **87**:188, 1948. Stein, I. F., Jr.; Meyer, K. A., and Steigmann, F.: Studies on Vagotomy in the Treatment of Peptic Ulcer: IV. Changes in Gastric Motility and the Effect of Drugs on Motility Following Complete Vagotomy, ibid. **87**:465, 1949. Stein, I. F., Jr., and Meyer, K. A.: Effect of Urecholine® on the Stomach, Intestine and Urinary Bladder, J. A. M. A. **140**:522 (June 11) 1949. Morrison, D. R.: A Case of Small Intestinal Stasis After Vagotomy Successfully Treated with Urecholine, Gastroenterology **12**:677, 1949. Gullickson, M. J., and Campbell, D. A.: Gastric Excretion of Neutral Red as Influenced by Vagotomy, ibid. **12**:454, 1949. Glass, G. B. J., and Boyd, L. J.: Response of Gastric-Dissolved Mucoprotein to Insulin: A New Test for Evaluation of Secretory Status of Fundal Glands and Integrity of Nervous Pathways to the Stomach, Bull. New York Acad. Med. **25**:459, 1949.

221. Asher, L. M.: The Gastric Mucosa After Vagotomy for Peptic Ulcer, Gastroenterology **11**:303, 1948.

222. Paulson, M., and Gladsden, E. S.: Gastroscopic Appearance Following Vagotomy with Significance of Observations in Relation to Gastric Innervation, J. A. M. A. **139**:151 (Jan. 15) 1949.

changes were not as pronounced as in those with vagotomy and subtotal gastrectomy. In both groups the stoma was patulous and relatively inactive. In the latter group redness and thickness of the mucosa were more apparent. Since similar mucosal changes are seen in similar circumstances in those without vagotomy, vagotomy per se does not protect against postoperative gastritis and jejunitis.

*Vagotomy—Favorable Results.*—Vagotomy without additional gastric surgical therapy was evaluated in 144 patients with "intractable" duodenal ulcer; one death occurred; observations extended from one to five and one-half years.[223] Eighty per cent of the group with transthoracic vagotomy and 86 per cent of that with transabdominal vagotomy secured an excellent result. The majority of patients with an unsatisfactory result were subsequently relieved by a gastroenterostomy. Failure of an ulcer to heal or its recurrence has usually been associated with incomplete vagotomy. Other workers have reported similar results.[224]

*Vagotomy and Other Surgical Procedures.*—Colp [225] states that gastroenterostomy combined with bilateral infradiphragmatic vagotomy is the preferred procedure in cases of duodenal ulcer unsuitable for subtotal gastrectomy. The immediate results of vagotomy in the treatment of

223. Dragstedt, L. R., and Camp, H. C.: Follow-Up of Gastric Vagotomy Alone in the Treatment of Peptic Ulcer, Gastroenterology **11**:460, 1948.

224. Grimson, K. S.; Rundles, R. W.; Baylin, G. J.; Taylor, H. M., and Linberg, E. J.: Vagotomy: Clinical Experiences During 4 Years, J. A. M. A. **139**:508 (Feb. 19) 1949. Moore, F. D.: Follow-Up of Vagotomy in Duodenal Ulcer, Gastroenterology **11**:442, 1948. Weinberg, J., and Kraus, A.: Early Results from Vagus Nerve Section in the Treatment of Duodenal Ulcer, West. J. Surg. **56**:577, 1948. Miller, E. M., and Olwin, J. H.: Results of Resection of the Vagus Nerve for Chronic Peptic Ulcer, Arch. Surg. **57**:353 (Sept.) 1948. Bergman, P. A.; French, S. W., and Seeley, S. F.: Experience with Vagotomy in the Treatment of Peptic Ulcer, Mil. Surgeon **104**:331, 1949. Ruffin, J. M.: The Ultimate Results of Vagotomy, Gastroenterology **11**:466, 1948. Winkelstein, A.: The Role of the Vagus Nerves in the Medical and Surgical Therapy of Peptic Ulcer, New York State J. Med. **48**:2153, 1948. Weinberg, J. A.; Campbell, G. W., and Voelker, R. B.: Vagus Nerve Section in the Treatment of Peptic Ulcer, J. Thoracic Surg. **17**:743, 1948. Johnson, F. H., and Kearney, E. A.: Vagus Neurectomy in Peptic Ulcer, U. S. Nav. M. Bull. **49**:475, 1949. Johnson, F. H., and Kearney, E. A.: Rapid Healing of a Perforating Peptic Ulcer Following Vagotomy, ibid. **48**:792, 1948. Soler-Roig, J.: Surgical Methods in the Treatment of Gastroduodenal Ulcers, Rev. españ. enferm. ap. digest. y nutrición **7**:749, 1948. Vaughn, A. M.: Vagotomy in the Treatment of Gastro-Intestinal Ulceration, Illinois M. J. **95**:343, 1949. Beattie, A. D.: The Physiological Basis of Vagotomy, Brit. M. J. **1**:607, 1949. Thorek, P.: Surgical Therapy in Gastroduodenal Ulcer, Rev. Gastroenterol. **16**:53, 1949.

225. Colp, R.: Surgical Treatment of Gastric, Duodenal and Gastrojejunal Ulcer, Including Present Status of Vagotomy, Bull. New York Acad. Med. **24**:755, 1948.

gastrojejunal ulceration following gastroenterostomy and subtotal gastrectomy have been excellent. Of 21 cases with unobstructed duodenal ulcer subjected to vagotomy alone, additional surgical measures were required in 7: in 5 for gastric dilatation and in 2 for duodenal ulcer. Vagotomy is not indicated in the treatment of gastric ulcer.

Vagotomy and partial gastrectomy were performed in 24 patients with "intractable" or complicated duodenal ulcer, 1 patient with duodenal and gastric ulcer and 2 patients with marginal ulcer; 2 deaths occurred [226]; immediate results on the remainder were encouraging. Most patients with gastric ulcer requiring operation should be treated by gastric resection rather than by vagotomy. Vagotomy for gastric ulcer is recommended when the ulcer is excised and examined microscopically or when the ulcer is so situated that it cannot be resected without performing a total gastrectomy or incurring undue risk.[227] Collins and his co-workers [228] favor bilateral vagotomy plus gastroenterostomy or pyloroplasty. Wilkinson and Sullivan [229] are not convinced that the addition of vagotomy to subtotal gastrectomy greatly increases the patient's chance for cure.

*Vagotomy—Restricted Application.*—Vagotomy is advocated only for peptic ulcer occurring after gastroenterostomy or gastrectomy [230]; some surgeons think that the procedure has only limited value.[231]

*Postvagotomy Management.*—Among 50 patients subjected to vagotomy with or without gastroenterostomy or subtotal gastric resection, no recurrent ulcerations were observed during the subsequent period of observation.[232] Fulness, nausea, vomiting and regurgitation

226. Hatch, F. F.; Nelson, W., and Bauerlein, T. C.: The Combined Procedure of Vagotomy and Partial Gastric Resection in the Treatment of Peptic Ulcer, Rocky Mountain M. J. **46**:460, 1949.

227. Crile, G., Jr., and Dempsey, W. S.: Treatment of Gastric Ulcer, Cleveland Clin. Quart. **15**:147, 1948.

228. Collins, E. C.; Crile, G., Jr., and Davis, J. B. Follow-Up of Vagotomy Plus Gastroenterostomy or Pyloroplasty for Ulcer, Gastroenterology **11**:453, 1948.

229. Wilkinson, S. A., and Sullivan, J. C.: Vagotomy Combined with Subtotal Gastrectomy, Gastroenterology **11**:457, 1948.

230. Govaerts, J., and van Geertruyden, J.: Application de la vagotomie au traitment de l'ulcère gastroduodénal, Acta gastro-enterol. belg., 1949, supp., p. 95. Delannoy, E., and Auguste, C.: Vagotomie et ulcus peptique postopératoire: Opinion sur les indications actuelles de la vagotomie, ibid. **12**:384, 1949. Blixenkrone-Møller, N.: Vagotomy in Peptic Ulcer, Nord. med. **39**:1629, 1948. Appleby, L. H.: An Assessment of the Results of Vagotomy, Canad. M. A. J. **59**:58, 1948.

231. Toller, P. A.; Localio, S. A., and Hinton, J. W.: The Late Effect of Vagus Nerve Resection for Peptic Ulcer, Am. Pract. **3**:539, 1949. Boller, V. R.: Die Vagotomie zur Behandlung der peptischen Geschwüre, Gastroenterologia **74**:280, 1948-1949. Weinberg, J. A.; Campbell, G. W., and Voelker, R. B.: Vagus Nerve Section in the Treatment of Peptic Ulcer, J. Thoracic Surg. **17**:743, 1948.

232. Paulson, M., and Gladsden, E. S.: Medical Management Following Vagotomy for Peptic Ulcer, M. Clin. North America **32**:1711, 1948.

were treated with urecholine® (urethane of beta-methylcholine chloride); reoperation was necessary in 2 instances because of gastric retention. The dumping syndrome was managed by elimination of bulky foods; hypoglycemia was controlled through a routine of frequent feedings.

*Recurrence After Vagotomy.*—Rob [233] reports an adequate resection of the vagus nerves (insulin test) with recurrent ulcer symptoms after six months.

*Vagotomy and Splanchnicectomy.*—Goethals-Borin [234] proposes combined use of vagotomy and splanchnicectomy. Supradiaphragmatic section of the splanchnic nerves was performed in 25 patients with peptic ulcer, based on the hypothesis that in peptic ulcer sympathicotonia is predominant and vagotonia secondary.[235] Twenty-four patients are reported as immediately relieved of symptoms; study of the long term results is in progress.

*Follow-Up Studies of Peptic Ulcer and Recurrence.*—The average length of time elapsed since separation from military service because of duodenal ulcer in 305 veterans was thirty-four months; 5 had undergone surgical treatment.[236] Roentgenograms at follow-up study revealed a crater in 22 per cent, irritable bulb in 11 per cent, deformed bulb in 41 per cent and normal appearance in 26 per cent. Symptoms of active ulcer were present in 60 per cent. Six per cent had had no recurrences; 9 per cent had no symptoms if they adhered to an ulcer diet; 12 per cent had rare, 30 per cent frequent and 43 per cent almost continuous symptoms. The ulcers of 38 per cent were classified as "intractable" to medical management. The high incidence of disability is attributed to the compensation factor, although improper ulcer management and emotional factors were thought to play a role.

A seven to ten year follow-up study was made of 687 patients with peptic ulcer.[237] The course appeared favorable in only 31 per cent of patients; only approximately half of these were entirely free from distress. The course was definitely serious in 40 per cent of the patients; 3.9 per cent died of peptic ulcer; 5.2 per cent had perforations. The

233. Rob, C. G.: Recurrence of Duodenal Ulcer 6 Months After Adequate Vagotomy, Lancet **2**:730, 1948.

234. Goethals-Borin, J.: Les énervations du système orthosympathique de l'estomac et du duodénum dans les ulcères gastroduodénaux, Acta gastro-enterol. belg., 1949, supp., p. 185.

235. Baumgartner, W.: Should Peptic Ulcer Be Treated by Means of Vagotomy or Splanchnicotomy? Gastroenterologia **74**:156, 1948-1949.

236. Hussar, A. E.: Duodenal Ulcer—A Follow-Up Study of 305 Veterans Discharged Because of Ulcer, Gastroenterology **11**:183, 1948.

237. Malmros, H., and Hiertonn, T.: Follow-Up of 687 Medically Treated Cases of Peptic Ulcer, Acta med. Scandinav. **133**:229, 1949.

course was more favorable in patients with gastric than with duodenal ulcer. A follow-up survey was made of patients treated for peptic ulcer in northern Norway during the periods Jan. 1, 1934 to June 30, 1940 and July 1, 1940 to June 30, 1945.[238] The results of medical treatment were poor. Less than one fourth were cured after routine hospital treatment in either period. An exception was found in the group with acute gastric ulcer; more than 50 per cent in this category in the war period were cured. Gastric resections were done in 84 patients, with a 6 per cent mortality; 32.2 per cent complained of digestive symptoms after resection.

Prevention of recurrences of peptic ulcer requires constant observation and a strict regimen. The four inciting causes for exacerbations are (1) physical or mental fatigue; (2) emotional disturbances; (3) dietary indiscretions; and (4) infections, particularly of the upper respiratory tract.[239]

*Electrolyte Disturbances.*—Burnett and associates[240] describe an interesting syndrome in 6 male patients who gave the common history of peptic ulcer or ulcer symptoms treated by excessive intake of milk and alkalis for many years. The syndrome is characterized by a history of prolonged and excessive intake of milk and absorbable alkali, hypercalcemia without hypercalciuria or hypophosphatemia, normal serum alkaline phosphatase, mild alkalosis, calcinosis manifested especially by an ocular lesion resembling band keratitis and improvement on a regimen low in milk and absorbable alkali. The following sequence of events is suggested: excessive intakes of milk (high in calcium and phosphorus) and alkalis, renal damage, tendency to fixation in urinary calcium excretion, hypercalcemia, tendency to supersaturation in respect to calcium phosphate and calcinosis. [The reviewers have encountered 2 patients, both men with hypertension and duodenal ulcer, who presented features such as these; the intake of alkali (calcium carbonate) immediately prior to the development of the syndrome was small.]

A patient showed alkalosis and hypopotassemia following the repair of a gastrojejunocolic fistula; therapy with potassium and ammonium chloride was followed by prompt clinical improvement.[241]

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238. Muri, J.: Localization and Results of Treatment of Peptic Ulcers, Nord. med. **4**:254, 1949.

239. Althausen, T. L.: Prevention of Recurrences in Peptic Ulcer, Ann. Int. Med. **30**:544, 1949.

240. Burnett, C. H.; Commons, R. R.; Albright, F., and Howard, J. E.: Hypercalcemia Without Hypercalcuria or Hypophosphatemia, Calcinosis, and Renal Insufficiency, New England J. Med. **240**:787, 1949.

241. Kennedy, T. J., Jr.; Winkley, J. H., and Dunning, M. F.: Gastric Alkalosis with Hypokalemia, Am. J. Med. **6**:790, 1949.

*Massive Hemorrhage.*—General Results: A total of 757 cases of bleeding ulcer is reviewed.[242] None of the patients was subjected to surgical treatment. The treatment consisted of blood transfusions, adequate fluids and a milk diet. Of 300 patients with massive hematemesis, 57 per cent had chronic duodenal ulcer, 14 per cent acute gastritis, 11 per cent chronic gastric ulcer, 8 per cent esophageal varices and 4 per cent chronic gastritis; in only 1.3 per cent was the bleeding due to gastric carcinoma; the mortality was 25 per cent.[243] In a subgroup of 74 patients treated by adequate replacement of blood, the mortality decreased to 4 per cent. Surgical intervention, use of an indwelling stomach tube with suction, gastric lavage and active gastric diagnostic studies were observed to increase mortality during the actively bleeding stage. Among 218 patients with bleeding peptic ulcer, the mortality rate was 54 per cent in those treated by starvation and 0 among those managed by the Meulengracht regimen.[244] Of the 136 patients treated medically, 12 died; of the 82 patients who were operated on after the hemorrhage had ceased or greatly decreased, 4 died. Bartels[245] concludes that the Meulengracht treatment is not superior to the Faber-Sippy type of regimen. In patients over 50 years of age operation is advised if bleeding persists for more than thirty-six to forty-eight hours. Fifty-seven consecutive patients with bleeding peptic ulcer were treated conservatively without fatality.[246]

Ninety-four per cent of deaths from massive hemorrhage were of persons more than 40 years of age; 82 per cent were of those over 50.[247] The mortality was approximately 2 per cent in patients treated by frequent feeding and blood transfusions. Among persons over the age of 50 with hematemesis from ulcer the mortality was 30 per cent. Less than 10 per cent of all patients with bleeding ulcer, but 70 per cent of all who died from exsanguination, were in this small group. Surgical therapy after the first hematemesis is advised for persons over 50 years of age with ulcer. Two hundred and eight of 305 patients with hematemesis admitted to the hospital as emergencies had a history of

242. Sinding-Larsen, C. M., and Tho, A.: Manifest Hemorrhage from Peptic Ulcers, Nord. med. **41**:251, 1949.

243. Costello, C.: Massive Hematemesis: Analysis of 300 Consecutive Cases, Ann. Surg. **129**:289, 1949.

244. Lewison, E. F.: The Treatment of Bleeding Peptic Ulcer, South. M. J. **41**:1031, 1948.

245. Bartels, E. D.: Prognosis and Treatment of Massive Hemorrhage from Gastric and Duodenal Ulcers, Acta med. Scandinav. (supp. 213) **131**:61, 1948.

246. Fisher, R. L., and Zukerman, M.: Bleeding Peptic Ulcer: A Review of 57 Consecutive Cases, Am. J. Med. **5**:503, 1948.

247. Pedersen, J.: Lethality Rate of Hematemesis and Melena Treated Non-Operatively (Meulengracht's Regimen) and Criteria for Surgical Intervention in Bleeding Peptic Ulcer, Gastroenterology **12**:597, 1949.

proved or probable chronic peptic ulcer.[248] The fatality rate of 19 per cent rose steeply in the middle and older age groups; recurrent bleeding was as frequent in the younger age groups as in the old. The mortality of bleeding gastric ulcer is higher than that of duodenal ulcer and rises further in older patients.[249] The total mortality in a group of 177 consecutive patients with moderate to severe hemorrhage from duodenal ulcer was 6.2 per cent[250]; 4 of 12 patients operated on for severe hemorrhage died.

Use of Thrombin: Topical thrombin administered perorally in several doses of 10,000 units in an isotonic solution controlled bleeding in 2 cases of gastric hemorrhage, one due to arterial erosion in peptic ulcer and one arising in acute gastritis.[251] Experience in treating 100 patients with bleeding from the upper part of the gastrointestinal tract indicated that thrombin and seventh-molar phosphate buffer administered by mouth or by intragastric tube may be a useful adjunct in therapy; however, the treatment is ineffective in many patients.[252]

Surgical Treatment: Hoerr and his co-workers[253] are of the opinion that the chief indication for operation is not the amount but the rate of bleeding, as evidenced by syncope or shock despite emergency medical treatment by continuous transfusions. A plan of treatment of massive hemorrhage from peptic ulcer consisted of rapid copious blood transfusions and gastric resection within twenty-four hours after the patient's admission to the hospital.[254]

*Jejunal Ulcer and Gastrojejunocolic Fistula.*—In the definitive treatment of gastrojejunal ulcer following gastroenterostomy, adequate gas-

248. Lewin, D. C., and Truelove, S.: Hematemesis: With Special Reference to Chronic Peptic Ulcer, Brit. M. J. **1**:383, 1949.

249. Sandusky, W. R., and Mayo, H. W., Jr.: The Management of Severe Bleeding from Gastric, Duodenal, and Jejunal Ulcers, South. Surgeon **15**:69, 1949.

250. Fraser, R. W., and West, J. P.: The Management of Bleeding Duodenal Ulcers, Ann. Surg. **129**:299, 1949.

251. Rogers, T. M.: Management of Gastric Hemorrhage Using Topical Thrombin, J. A. M. A. **137**:1035 (July 17) 1948.

252. Daly, B. M.; Johnston, C. G., and Pemberthy, G. C.: The Management of Patients with Bleedings from the Upper Gastro-Intestinal Tract with Buffer and Thrombin Solution, Ann. Surg. **129**:832, 1949.

253. Hoerr, S. O.; Dunphy, J. E., and Gray, S. J.: The Place of Surgery in the Emergency Treatment of Acute Massive, Upper Gastrointestinal Hemorrhage, Surg., Gynec. & Obst. **87**:338, 1948. Dunphy, J. E., and Hoerr, S. O.: The Indication for Emergency Operation in Severe Hemorrhage from Gastric or Duodenal Ulcer, Surgery **24**: 1948.

254. Stewart, J. D.; Massover, A. J.; Potter, W. H., and Schaer, S. M.: Massive Hemorrhage from Gastroduodenal Ulcer, Surgery **24**:239, 1948. Stewart, J. D.; Schaer, S. M.; Potter, W. H., and Massover, A. J.: Management of Massively Bleeding Peptic Ulcer, Ann. Surg. **128**:791, 1948.

tric resection probably offers the best chance of cure; vagotomy affords a promising mode of treatment for recurrence in patients who already have been subjected to acceptable resection.[255] Twenty-two cases of gastrojejunocolic fistula which occurred an average of six years two months after gastroenterostomy are reported; after surgical repair the fistula recurred in 2 cases.[256] Gastrectomy is the preferred treatment of gastrojejunal fistula,[257] but, in the opinion of Faxon and Schock,[258] it should be supplemented with transthoracic vagotomy.

*Perforation.*—Surgical Treatment and Results: Among 362 consecutive patients with acute perforation of gastric and small bowel ulcerations, 318 were treated surgically, with an operative mortality of 18.2 per cent.[259] The mortality was 5.8 per cent when operation was performed within six hours and rose to 54.5 per cent when operation was performed after twenty-hour hours.

Perforation occurred in 10 per cent of cases of benign gastric ulcer during a ten year period and in 1 per cent of cases with malignant gastric lesions encountered during a forty year period.[260] In a series of 200 consecutive patients with perforated gastric and duodenal ulcers covering a twelve year period, the over-all mortality was 26 per cent; mortality was 20 per cent for those who underwent operation. The mortality rate rose with the age of the patients.[261] In 336 cases of acute gastroduodenal perforation the mortality rate progressively declined from 21 to 10.7 per cent in the twelve year period, 1935 to 1946.[262] With continued penicillin and sulfadiazine therapy the mortality dropped to 0 in patients treated in the first six hours and to 7.5 per cent in patients treated between six and twelve hours after perforation.

Penicillin was used postoperatively and resulted in a mortality of 4.8 per cent among 42 cases of perforated peptic ulcer and of 1 per cent

255. Ransom, H. K.: Treatment of Jejunal Ulcer: A Comparative Follow-Up Study, Arch. Surg. **58**:684 (May) 1949.

256. Lawton, S. E., and Marks, A. R.: Gastrojejunocolic Fistula, Arch. Surg. **58**:762 (June) 1949. Isaacs, B.: Gastro-Jejunocolic and Jejunocolic Fistula, Glasgow M. J. **30**:82, 1949.

257. Klingenstein, P.: Surgical Management of Gastro-Jejunal Fistula, J. Mt. Sinai Hosp. **14**:449, 1948.

258. Faxon, H. H., and Schock, W. G., Jr.: Gastrojejunocolic Fistula, New England J. Med. **240**:81, 1949.

259. Luer, C. A.: Acute Perforation of Stomach and Small Bowel Ulcerations, Surgery **25**:404, 1949.

260. Shellito, J. G., and Rivers, A. B.: Gastric Perforation: A Clinicopathologic Study, Gastroenterology **12**:919, 1949.

261. Shipley, E. R., and Walker, J. H.: Perforated Gastric and Duodenal Ulcers, Am. J. Surg. **77**:329, 1949.

262. McElhinney, W. T., and Holzer, C. E., Jr.: Factors Influencing Mortality from Acute Perforated Peptic Ulcers, Surg., Gynec. & Obst. **87**:85, 1948.

among 97 cases of perforated appendix.[263] The pronounced decrease in the operative mortality after suture of perforated gastric ulcer is attributed to the use of chemotherapy, modern methods of anesthetization and skilful preoperative and postoperative treatment.[264]

Nonoperative Treatment: Thirty-four patients with perforated duodenal ulcer were treated conservatively without fatality.[265] The only complications were pleural effusion in 1 patient and subphrenic abscess in 2. The essential features in the treatment are continuous gastric decompression, intravenous administration of fluids and administration of penicillin and sulfadiazine.

### DUODENUM

*Motility.*—Douglas[266] reported that the common type of activity of the duodenum in dogs was a rapid propulsive wave with a uniform frequency of between 17 and 19 per minute. Fasting usually produced quiescence, and subsequent feeding induced a rapid motor response. Present evidence, together with previously obtained information, suggests that (*a*) after the taking of food in the fasting animal, a wave of excitation passes down the entire length of the small intestine from duodenum to ileum and (*b*) there appear to be two zones of rhythmic frequency in the small intestine of the dog, an upper zone consisting of duodenum and jejunum in which the frequency is of the order of 17 to 19 contractions per minute and a lower zone in which the frequency is between 11 and 14 contractions per minute. In dogs, the most consistent response of the circular muscle of the duodenum to morphine was an increase in many phases of activity; frequently there was a decrease in or abolition of longitudinal muscle activity.[267]

*Bacteriologic Examination.*—In patients with achlorhydria the duodenal juice and bile contain Escherichia coli, streptococci and staphylococci.[268]

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263. Brown, R. B., and Andrus, D. L.: Penicillin in the Postoperative Treatment of Peptic Ulcer with Perforation and Appendicitis with Perforation, Ann. Surg. **128**:57, 1948.

264. Christoffersen, J. C., and Mortens, J.: Change in Operative Mortality After Suture of Perforated Gastric Ulcer, Ugesk. f. læger **111**:113, 1949.

265. Seeley, S. F.; Hogan, E.; Henry, J. R., and Bertram, H. F.: Non-Operative Treatment of Perforated Duodenal Ulcer, Bull. U. S. Army M. Dept. **9**:124, 1949.

266. Douglas, D. M.: The Activity of the Duodenum, J. Physiol. **107**:472, 1948.

267. Loomis, T.: Response of the Duodenum to Morphine, Proc. Soc. Exper. Biol. & Med. **69**:146, 1948.

268. Tomenius, J.: Bacteriologic Examination of the Duodenal Content with the Aid of a Special Tube, Gastroenterology **12**:623, 1949.

*Diverticula.*—Among 32 cases of duodenal diverticula, the diverticulum was considered nonproductive of symptoms in 14.[269] Improvement is reported in 8 of 14 patients treated medically. Gastrointestinal distress was relieved in 3 patients after surgical extirpation of duodenal diverticula; in 1 patient the diverticulum contained an ulcer. The authors believe that the majority of duodenal diverticula do not produce symptoms and require no treatment.[270] Only 5 instances of perforation of duodenal diverticula were found in the English and American literature; one case is added in which the perforated diverticulum in the second portion of the duodenum was excised successfully.[271]

*Tumors.*—A primary carcinoma of the duodenum was diagnosed as carcinoma of the intestinal tract by the finding of malignant cells in stains of duodenal drainage.[272] Three cases of gastrointestinal carcinoma interpreted as originating in the duodenal bulb are reported; the findings clinically and roentgenographically could not be distinguished from those of benign peptic ulcer.[273]

### SMALL INTESTINE

*Motility—Antispasmodics.*—Exteriorized skin-covered loops of jejunum and ileum were studied with reference to their rhythmic contractions and their motor response after feeding.[274] Motor-feeding response occurred more rapidly in loops nearer the pylorus than in more distally located loops. Use of atropine failed to block the action of acetylcholine and cholinesterase inhibitors in studies of the isolated ileum of various animals.[275]

An improved apparatus for recording intestinal motility is described.[276] By means of this arrangement, as studied in 12 patients,

269. Dunstan, S. M.; Lowance, M. I., and Jones, E. C.: Clinical Importance of Duodenal Diverticula, South. M. J. **42**:460, 1949.

270. Conti, J. G., Jr.; Foltz, T. P., and Stevens, G. A.: Surgical and Roentgenologic Aspects of Duodenal Diverticula, J. A. M. A. **138**:403 (Oct. 9) 1948.

271. Byerly, W. L., Jr.: Duodenal Diverticulitis with Perforation, Surgery **25**:441, 1949.

272. Mackenzie, L. L., and Miller, H. B.: Primary Carcinoma of the Duodenum, Gastroenterology **12**:309, 1949.

273. Chassin, J. L., and Hinton, J. W.: Primary Carcinoma of the Duodenal Bulb Mimicking Duodenal Ulcer, Gastroenterology **12**:312, 1949.

274. Watkins, D. H., and Mann, F. C.: Motor Responses of Spatially Transposed Intestinal Loops, Surgery **25**:393, 1949.

275. Flesch, P., and Kun, E.: Action of Acetylcholine, Histamine and Cholinesterase Inhibitors on Isolated Ileum in Relation to Its Survival Time, Proc. Soc. Exper. Biol. & Med. **69**:166, 1948.

276. Posey, E. L., Jr.; Dearing, W. H.; Sauer, W. G.; Bargen, J. A., and Code, C. F.: The Recording of Intestinal Motility, Proc. Staff Meet., Mayo Clin. **23**:297, 1948.

administration of neostigmine (prostigmin®) was found to shift motility toward propulsion.[277]

Tetraethylammonium chloride administered intravenously promptly inhibited motility in 4 subjects; the individual response varied widely.[278] Posey and his associates[279] studied the effect of amethone® (3-[β-diethylaminoethyl]-3-phenyl-2-benzofuranone hydrochloride), octin® (methylamino-iso-octene), NU-72-4D (2,6-di[P-methoxyphenethyl]-1-methylpiperidine hydrochloride), pavatrine® (β-diethylaminoethyl fluorine-9-carboxylate hydrochloride), syntropan® (amprotropine hydrochloride), trasentine® (adiphenine hydrochloride), phenobarbital, ephedrine and atropine given by mouth in the usual therapeutic doses. None of the synthetic preparations seemed practical. Atropine was consistently effective in depressing or abolishing motility; it had no effect on tone. Ephedrine reduced tone in 2 of 4 cases without altering motility. Dibutoline possesses both a smooth muscle–inhibiting action and an antiacetylcholine action.[280] Side effects have been chiefly moderate dryness of the mouth and slight diminution of ocular accommodation following the usual 10 to 20 mg. subcutaneous dose. The short duration of its action limits the usefulness of the drug. The effects of syntropan® were somewhat similar.[281] Profenil (phenylpropylethyl amine) is described as inhibiting smooth muscle contraction, reducing peristalsis, decreasing acid and pepsin secretion and producing vasodilatation of the gastrointestinal mucosa.[282]

*Absorption.*—Althausen[283] states that hormones of the adrenal cortex, the hypophysis and the ovaries exert their effect on intestinal absorption indirectly, while the thyroid hormone has a direct stimulating effect on the intestinal absorption of carbohydrates and fats. The effect

277. McMahon, J. M.; Code, J. J.; Sauer, W. G., and Bargen, J. A.: A Study of the Action of Prostigmine on the Bowel of Human Beings, Gastroenterology **12**:970, 1949.

278. Posey, E. L.; Brown, H. S., and Bargen, J. A.: The Response of Human Intestinal Motility to Tetraethyl Ammonium Chloride, Gastroenterology **11**:83, 1948.

279. Posey, E. L., Jr.; Bargen, J. A.; Dearing, W. H., and Code, C. F.: The Effects of Certain So-Called Antispasmodics on Intestinal Motility, Gastroenterology **11**:344, 1948.

280. Marquardt, G. H.; Case, J. T.; Cummings, G. M., Jr., and Grossman, M. I.: Further Clinical Observation on the Use of Dibutoline, A New Antispasmodic Drug, Am. J. M. Sc. **216**:203, 1948.

281. Lorber, S. H., and Machella, T. E.: The Effect of Syntropan on the Motor Activities of the Human Gastrointestinal Tract and on Gastric Acidity, Gastroenterology **12**:57, 1949.

282. Nasio, J.: Il profenil come antispastico gastro-intestinale, Minerva med. **2**:454, 1948.

283. Althausen, T. L.: Hormonal and Vitamin Factors in Intestinal Absorption, Gastroenterology **12**:467, 1949.

of the thyroid hormone is mediated through phosphorylation. Vitamin B complex is indispensable for normal absorption of glucose in the intestine. It is suggested that the thyroid hormone controls preferential absorption in the intestine through activation of the oxidative enzyme systems in which several B vitamins play a dominant part.

*Roentgen Observations.*—Transit time for a barium sulfate meal through the small intestine is shortened to an hour or less when isotonic sodium chloride solution is used as a vehicle and is followed by draughts of ice cold isotonic sodium chloride solution.[284] In many cases the mucosal pattern is more clearly delineated and the small intestine is more adequately filled with contrast medium.

Segmentation of the barium sulfate suspension in the small intestine (so-called deficiency pattern) was induced in normal human subjects by the administration of hypertonic solutions.[285] Mucus-containing gastric or duodenal juice caused immediate and complete flocculation of the barium sulfate suspension. These observations indicate that the segmentation pattern is not necessarily associated with vitamin deficiencies or disordered motor function of the intestinal wall.[286] Spasticity and hypermotility of the small intestine and delay in the transport of barium sulfate, comparable to the changes observed in nutritional disorders, may be observed in elderly persons.[286]

The mucosal pattern of the terminal portion of the ileum in symptom-free children, as demonstrated by barium sulfate enema, differs from that of most adults in that it presents a cobblestone appearance perhaps attributable to aggregations of normal lymphoid tissue in the mucous membrane.[287]

*Meckel's Diverticulum.*—Among 143 patients with verified Meckel's diverticulum, 43 had pathologic changes directly referred to the diverticula; of these 16 had ulcerations and 13 intestinal obstruction.[288]

*Regional Enteritis.*—The pathologic changes are described in detail by Owens.[289] Inclusion bodies in the giant cells noted in 2 cases of

284. Weintraub, S., and Williams, R. G.: A Rapid Method of Roentgenologic Examination of the Small Intestine: A Preliminary Report, Am. J. Roentgenol. **61**:45, 1949.

285. Frazer, A. C.; French, J. M., and Thompson, M. D.: Radiographic Studies Showing the Induction of a Segmentation Pattern in the Small Intestine in Normal Human Subjects, Brit. J. Radiol. **22**:123, 1949.

286. Jingmann, H. J., and Cosin, L.: Some Observations upon the Radiology of the Small Intestine in Old Age, Brit. J. Radiol. **22**:325, 1949.

287. Wells, J.: The Mucosal Pattern of the Terminal Ileum in Children, Radiology **51**:305, 1948.

288. Owen, J. K., and Finney, G. G.: Surgical Aspect of Meckel's Diverticulum, South. M. J. **42**:98, 1949.

289. Owens, F. M., Jr.: Regional Enteritis: Further Pathological Observations, Arch. Surg. **57**:195 (Aug.) 1948.

cicatrizing enteritis were found by physical and chemical examination to be inorganic calcium salts; their origin is attributed to focal abnormalities of the cytoplasm of giant cells which attracted calcium salts.[290]

A regional ileitis of benign prognosis and of obscure origin is described which is thought to be different from Crohn's disease in that it does not lead to ulceration, fibrosis, stenosis, fistula and chronic illness. Roentgenographic examination demonstrates a honeycomb pattern of the ileum.[291] Cicatrizing enteritis, with fibrosis, chronic inflammation and calcification, is described in a newborn infant; since a calcified mass was found in the abdominal cavity when the child was 3 days old and because fibrosis, chronic inflammation and calcium deposits were observed in the wall and lumen of the ileum, the process was considered to have begun in utero.[292]

A series of 47 patients with regional enteritis included 20 with acute attacks and 1 death and 27 with more gradual development of the disease and 9 deaths. Loria [293] states that treatment of acute regional enteritis gradually has become more conservative; chronic conditions remain unpredictable and usually require radical surgical treatment which is frequently disappointing. A survey of 55 cases of regional enteritis indicated to Rossmiller and Crile [294] that medical treatment should be confined to the patients with acute and mild chronic attacks and to those with diffuse involvement. Surgical treatment is indicated for patients with chronic enteritis and moderate to severe symptoms, with diffuse enteritis and with complications, such as fistula or obstruction. Anastomosis, with division of the bowel and exclusion of the involved segment, usually results in remission of symptoms.

*Tuberculous Enteritis.*—Striking improvement in all manifestations of tuberculous enteritis is reported in 33 patients treated with streptomycin.[295]

*Acute Pseudomembranous Enteritis.*—Acute pseudomembranous inflammation of the mucosa and submucosa of the gastrointestinal tract

290. Warren, S., and Sommers, S. C.: Giant-Cell Inclusions in Cicatrizing Enteritis, Proc. Soc. Exper. Biol. & Med. **68**:461, 1948.

291. Calder, E.: Radiological Aspects of Recoverable Regional Ileitis and Its Relationship to Crohn's Disease, Glasgow M. J. **30**:65, 1949.

292. Fetter, J. S., and Mills, W. L.: Regional Ileitis (Cicatrizing Enteritis) of Prenatal Origin, Am. J. Roentgenol. **61**:366, 1949.

293. Loria, L. L.: Regional Enteritis, South. Surgeon **14**:542, 1948.

294. Rossmiller, H. R., and Crile, G., Jr.: Surgical Treatment of Regional Enteritis, S. Clin. North America **28**:1139, 1948.

295. Mason, E. F.; Kridelbaugh, W. W.; Crouch, W. H., and Ward, M.: Streptomycin in the Treatment of Tuberculous Enteritis: A Report of 33 Cases, Am. J. M. Sc. **217**:28, 1949.

following surgical intervention was encountered in 23 patients.[296] The most pronounced histologic changes were hyperemia and vascular engorgement of the submucosa. The clinical features included circulatory collapse, diffuse cramping abdominal pain and frequent bowel movements or enteric stomal discharges. Two patients who survived received chemotherapy, blood, plasma and fluids parenterally.

Focal and diffuse lesions of the digestive tract, pancreas, liver, kidneys and parotid glands occur in a variety of clinical conditions accompanied with shock. The intestinal lesions consist of small foci of thickening and congestion; with greater severity, the lesions fuse and become hemorrhagic, eventually resulting in sloughing of the mucosa and perforation.[297]

*Necrotizing Jejunitis.*—Fifty-five cases of an apparently new syndrome, necrotizing jejunitis, recognized recently in Germany, are described by Wigand.[298] References are given to the literature for details of the clinical picture; the illness in 37 patients was classified as severe, and of these 27 died; in the "mild" group of 18 patients only 1 died. The diagnosis in 33 patients was established at operation or necropsy and in the remainder on clinical and roentgenologic evidence. The age incidence ranged from 18 to 80 years, with an average of 55. There were 45 men and 10 women. The majority of cases occurred from August to October 1946. The disease appears either as an enteritis or as an ileus. Fever was present in approximately 50 per cent of the patients; the temperature never exceeded 103 F.

Fick and Wolken [299] encountered 18 cases of necrotic jejunitis from 1944 to 1948 in northern Germany. The clinical features were similar to those previously described. Operation or necropsy revealed severe inflammation and necrosis usually involving an extensive section of jejunum. The histologic picture is that of generalized necrosis of varying degree. Necrotic jejunitis does not resemble regional enteritis. In a series of 147 cases observed in Berlin from July to September 1949, the mortality rate was 42.8 per cent.[300]

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296. Dixon, C. F., and Weismann, R. E.: Acute Pseudomembranous Enteritis or Enterocolitis: A Complication Following Intestinal Surgery, S. Clin. North America **28**:999, 1948.

297. Penner, A., and Druckerman, L. J.: Enterocolitis as a Postoperative Complication and Its Significance, Gastroenterology **11**:478, 1948.

298. Wigand, H.: Clinical Features of Necrotizing Jejunitis with Special Reference to Mild Forms, Ztschr. f. d. ges. inn. Med. **2**:570, 1947.

299. Fick, K. A., and Wolken, A. P.: Necrotic Jejunitis, Lancet **1**:519, 1949.

300. Anders, W.: Necrotizing Enteritis in Berlin, Therap. d. Gegenwart **10**:222, 1948.

Necropsy or biopsy studies were obtained in an additional 133 cases; bacteriologic studies were made in approximately 100 cases.[301] Four stages of the disease are described: (*a*) catarrhal serous enteritis; (*b*) necrotizing enteritis; (*c*) ulcerous enteritis, and (*d*) chronic suppurative granulomatous enteritis. A virus or both virus and bacteria may be implicated in the causation. The mortality rate varied from 14 to 40 per cent. Hormann[302] reports on 88 patients with necrotizing enteritis, verified at autopsy. Their cases were part of an epidemic of vast extent with many abortive cases. The causation has not been established, although the possibility of an air-borne enterotropic virus is mentioned. Jeckels, in discussing this paper, states that the disease was unknown in Lübeck until 1946; since then 134 cases have been encountered. The characteristic histologic change is necrosis of arterial walls in the submucosa. Several workers have isolated Clostridium perfringens from the intestine. Resection of the diseased bowel has been effective in some cases. The autopsy observations in 8 cases consisted of zones of hemorrhagic necrosis, often in the form of cuffs, separated by healthy areas.[303] The lesions may be limited to the mucosa or may also involve the submucosa. The mesenteric lymph nodes are enlarged.

Specimens obtained from 8 patients post mortem and from 1 surviving patient with enteritis necroticans yielded an organism resembling Clostridium welchii (Cl. perfringens).[304] This organism, termed Cl. welchii type F, was lethal for guinea pigs when injected intramuscularly or intravenously, but not when given orally. Lesions similar to enteritis necroticans were produced by injecting the organism into the lumen of the intestine. In vitro tests indicated that Cl. welchii type F is inhibited by 10 units of penicillin per milliliter and is sensitive to sulfamylon® (4-aminomethyl-benzene sulfonamide hydrochloride), marbadal® (marfanil salt of sulfathiourea) and supronal® (a mixture of sulfamerazine and marbadal®), which inhibit growth at a dilution of 1 in 10,000; sulfadiazine has no effect on growth. Since the necrotizing action of Cl. welchii type F is readily inhibited by serums containing Cl. welchii B antitoxin, the lesion is attributed to B toxin.[305] Approximately one sixth of normal persons in Hamburg, Germany, carried the organism

301. Kloos, K.: Esophago-Gastro-Enterocolitis (Intestinitis Gravis) with Necrotic Tendencies: High Incidence During Period from 1946 to 1948, Deutsche Ztschr. f. Verdauungskr. **9**:141, 1949.

302. Hormann: Etiology of Necrotizing Enteritis, Klin. Wchnschr. **26**:319, 1948.

303. Kulpe, W.: Necrotizing Jejunitis as an Enteric Intoxication, Deutsche Gesundheitswesen **3**:268, 1948.

304. Zeissler, J., and Rassfeld-Sternberg, L.: Enteritis Necroticans Due to Clostridium Welchii Type F, Brit. M. J. **1**:267, 1949.

305. Oakley, C. L.: The Toxins of Cl. Welchii Type F, Brit. M. J. **1**:269, 1949.

Cl. welchii type F in their feces; these strains were less pathogenic for animals than were those isolated from persons with enteritis necroticans.[306] Other writers have described additional cases of this puzzling disease.[307]

*Intestinal Lipodystrophy (Whipple's Disease).*—Important information regarding the pathologic features of this disorder is provided by recent studies.[308]

*Steatorrhea and Sprue.*—The epidemiologic characteristics, clinical manifestations and laboratory features of 1,069 cases of tropical sprue among Italian prisoners of war in a concentration camp in India are described by Stefanini.[309] Complete remission following dietetic and/or parenteral liver therapy occurred in 69.4 per cent of 62 patients with sprue in India, later followed for two years in England; there was a definite relapse in 16.1 per cent of the patients.[310]

Fat excretion and nitrogen loss were measured in 6 normal subjects, 4 patients with steatorrhea and 3 other patients.[311] The estimated probable upper normal limit of fat excretion in four days on a 70 Gm. fat diet was 23 Gm. Estimation of the four day excretion of fat is usually adequate for the diagnosis of steatorrhea, but twelve day studies must be made when therapy is to be evaluated. High fecal nitrogen loss in pancreatic steatorrhea distinguishes it from steatorrhea of intestinal origin. Fat absorption in a patient with tropical sprue approached normal after treatment with folic acid, liver and yeast. After several months of folic acid treatment of 2 patients with idiopathic steatorrhea. there was no change in fat absorption.

306. Hain, E.: On the Occurrence of Cl. Welchii Type F in Normal Stools, Brit. M. J. **1**:271, 1949.

307. Husebye, O. W.: On Roentgenological Diagnosis of Jejunitis Acuta Phlegmonosa, Acta radiol. **29**:71, 1948; A Case of Chronic, Non-Specific Jejunitis and Stenosis, ibid. **29**:516, 1948. Olivier, C.: Les jejunitis aigues, Presse med. **16**:215, 1949. de Aleneida, A. D., and Filho, J. S. H.: Necrotizing and Ulcerating Enteritis, Rev. paulista de med. **34**:293, 1949.

308. Newman, B., and Pope, R. H.: A Case of Intestinal Lipodystrophy (Whipple's Disease) Simulating Boeck's Sarcoid, Gastroenterology **11**:120, 1948. Rutishauser, E.; Demole, M., and Mach, R. S.: Sprue Due to Intestinal Lipostasis (Intestinal Lipodystrophy, Whipple's Disease), Rev. méd. de la Suisse Rom. **68**:573, 1948. Jones, F. A., and Paulley, J. W.: Intestinal Lipodystrophy (Whipple's Disease), Lancet **1**:214, 1949.

309. Stefanini, M.: Clinical Features and Pathogenesis of Tropical Sprue, Medicine **27**:379, 1948.

310. Keele, K. D.: The Prognosis and Treatment of Sprue in India, Brit. M. J. **1**:986, 1949.

311. Fourman, L. P. R.; Higgins, G., and Quelch, P.: Investigation and Diagnosis of Steatorrhea, Clin. Sc. **7**:109, 1948.

Chylomicron counts were done on 11 normal subjects and 28 patients with sprue.[312] The chylomicron curve in the normal persons increased and diminished when more or less fat was given, suggesting that chylomicrons represent one form of absorbed fat. In patients with sprue, little relation was seen between the height of the curve and the degree of steatorrhea. Concurrent chylomicrons represent a variable fraction of the absorbed neutral fat. It is concluded that a small proportion of the total fat is absorbed without splitting as finely emulsified neutral fat. While all patients with sprue have a defective absorption of split fat, impairment of neutral fat absorption, as judged by chylomicron count, is present in only a few.

Moderate edema with a normal total serum protein level was observed in 10 per cent of patients with tropical sprue.[313] In 45 per cent of these a conspicuous extension of the edema occurred early in treatment, in direct relationship to the occurrence of the reticulocyte crisis and a noticeable drop in the total serum protein level. Regression of edema occurred almost critically twenty to twenty-five days after the beginning of the treatment, concomitantly with a rise in the serum proteins. It is tentatively suggested that the decrease in serum proteins initially in treatment may be related to active erythropoiesis. The proteolytic activity of the gastric juice has been studied and found to be greatly diminished during relapses of sprue.[314] Among 7 patients with steatorrhea and anemia, virtual cessation of pancreatic secretion, as measured by the secretin test, was noted in 1; 1 patient gave low normal values, and the response in 5 was normal.[315]

Posey and Bargen [316] discuss the problem of jejunoileac insufficiency after resection of small bowel.

Administration of folic acid seemed to produce striking improvement in the roentgenographic appearance of the small intestine without improvement of fat absorption.[317] Vitamin $B_{12}$, per unit of weight, is reported to be more effective in treating human disease than any com-

312. Fourman, L. P. R.: The Chylomicron Count in Normal Subjects and Patients with Sprue, Tr. Roy. Soc. Trop. Med. & Hyg. **41**:537, 1948.

313. Stefanini, M.: Hypoproteinemia and Edema in the Course of Tropical Sprue, Gastroenterology **11**:50, 1948.

314. Fox, H. J.: Observations on the Proteolytic Activity in Vitro at Neutral Reaction of Gastric Juice from Patients with Sprue, J. Clin. Investigation **28**:687, 1949.

315. Newsome, J.: The Secretin Test of Pancreatic Function and Its Use in Steatorrhea, Gastroenterologia **74**:258, 1948-1949.

316. Posey, E. L., Jr., and Bargen, J. A.: Jejuno-Iliac Insufficiency: Its Relation to the Sprue Syndrome, S. Clin. North America **28**:903, 1948.

317. Ferguson, J. W., and Calder, E.: Folic Acid in Non-Tropical Sprue with Particular Reference to Fat Absorption and Radiological Appearances of the Small Intestine, Glasgow M. J. **29**:341, 1948.

pound employed to date.[318] Three patients with tropical sprue were maintained in good health with massive doses of thymine.[319]

Twenty-two infants and children considered to be suffering from celiac disease were treated with a low fat, high protein diet, liver extract and vitamins; folic acid was then added for a comparable period but without additional benefit.[320]

*Absorption of Fat.*—Polyoxyethylene sorbitan monooleate (sorethytan [20] monooleate) added to the diet increases the absorption of fat and fat-soluble substances in man, probably because of its ability to lower surface tension.[321]

*Intussusception.*—In 95 per cent of 610 instances of intussusception in children the causation was unknown; the optimum treatment is surgical reduction after rapid preoperative preparation.[322] The mortality rate in recent years has decreased to 2.7 per cent.

*Intestinal Obstruction.*—Evans [323] reviews the subject of alimentary obstructions in infancy with special reference to roentgenologic diagnosis. Hypertrophic pyloric stenosis accounted for half the cases observed, with intussusception and atresia at various levels next commonest. Strangulated hernia, meconium ileus, congenital bands and volvulus were also encountered. Atresias and meconium ileus predominate in the first two weeks of life; hypertrophic pyloric stenosis is usually found from the second to the tenth week and intussusception from the second to the eighth month. Carefully conducted contrast studies with barium sulfate solution led to a correct diagnosis in 7 cases of incomplete congenital alimentary obstruction in the newborn.[324] Frequent and intense vomiting is the most important symptom of gastrointestinal anomaly.[325]

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318. Spies, T. D., and Saurez, R. M.: Response of Tropical Sprue to Vitamin $B_{12}$, Blood **3**:1213, 1948.

319. Lopez, G. G.; Milanes, F.; Toca, R. L.; Aramburn, T., and Spies, T. D.: The Maintenance of Patients with Tropical Sprue by Means of Massive Doses of Synthetic 5-Methyl Uracil (Thymine), Am. J. M. Sc. **216**:270, 1948.

320. Hay, J. D.: Folic Acid in Coeliac Diseases, Arch. Dis. Childhood **23**:220, 1948.

321. Jones, C. M.; Culver, P. J.; Drummey, G. D., and Ryan, A. E.: Modification of Fat Absorption in the Digestive Tract by the Use of an Emulsifying Agent, Ann. Int. Med. **29**:1, 1948. Brown, C. H.: Method of Intensive Treatment of Sprue, Cleveland Clin. Quart. **16**:52, 1949.

322. Gross, R. E., and Ware, P. F.: Intussusception in Childhood: Experiences from 610 Cases, New England J. Med. **239**:645, 1948.

323. Evans, W. A.: Obstructions of the Alimentary Tract in Infancy, Radiology **51**:23, 1948.

324. Baeyer, E. V.: Diagnosis of Congenital Obstruction of the Stomach and Small Intestine in the Newborn, Radiology **52**:157, 1949.

325. Sawyer, C. D.: Gastrointestinal Anomalies, New York State J. Med. **49**:523, 1949.

The serum potassium was reduced in 15 patients with vomiting due to acute intestinal obstruction, and it decreased further following therapy with saline and dextrose solution.[326] The electrocardiographic changes included lengthening of the Q-T interval, depression of the S-T segment, lowered or inverted T waves and the presence of U waves. The parenteral administration of potassium chloride in quantities of 100 to 700 cc. of a 1.14 per cent solution during periods of one-half to two and one-half hours corrected the electrolyte disturbance and the electrocardiographic abnormalities.

Coller and Buxton [327] relate the high mortality rate among patients with mechanical obstruction of the small bowel to delay in diagnosis. Mechanical adhesions and cancer were the most frequent causes of obstruction in 148 consecutive cases of bowel obstruction; the over-all mortality was 26 per cent for the patients in whom operation was done.[328] The mortality rate among patients over the age of 60 with 80 complete acute intestinal obstructions was 44.7 per cent.[329]

A mattress with a hole is designed to free the skin from contact with fistula or ileostomy drainage in patients with excoriation of the skin.[330] A simple nonirritating latex tube, suitable for purposes of prolonged feeding, is available.[331] A synthetic nutritive mixture for jejunostomy feeding, containing partially hydrolyzed proteins, dextrins and a low fat content, does not induce motor disturbance and permits gain in weight even when the jejunostomy feeding is continued for long periods.[332]

Wild [333] discusses in detail the design of long intestinal tubes and indicates lines of further development; the use of two holes distal to the balloon is recommended. A mercury-weighted tube for intestinal decompression is described by French authors.[334] A hand pump in a

326. Bellet, S.; Nadler, C. S.; Gazes, P. C., and Lanning, M.: Effect of Vomiting Due to Intestinal Obstruction on the Serum Potassium, Gastroenterology **12**:49, 1949; Am. J. Med. **6**:714, 1949.

327. Coller, F. A., and Buxton, R. W.: Acute Obstruction of the Small Bowel, J. A. M. A. **140**:135 (May 14) 1949.

328. Skjold, A. C.: Bowel Obstruction: An Analysis of 148 Cases, Minnesota Med. **31**:52, 1948.

329. Haley, H. B., and Jackson, A. S.: Acute Intestinal Obstruction in the Patient Over 60 Years, Wisconsin M. J. **47**:1180, 1948.

330. Dempsey, W. S., and Jones, T. E.: A Mattress for Patients with Bowel Fistula, Surgery **25**:117, 1949.

331. Glenn, W. W. L.: A Simple Non-Irritating Tube for Feeding Purposes, Gastroenterology **12**:248, 1949.

332. Hollander, F., and Soben, H. A.: A Modified Synthetic Predigested Aliment for Protracted Jejunostomy Feeding, Surgery **25**:580, 1949.

333. Wild, J. J.: The Design and Management of Long Intestinal Tubes, Surgery **25**:779, 1949.

334. Brocq, P., and Eudel, F.: Les sondes à lumière unique et lestées au mercure dans l'intubation du grêle et du côlon, Presse méd. **57**:258, 1949.

welded steel tank is utilized for applying suction to tubes in the gastrointestinal tract.[335] Distention of the latex bag of an intestinal tube may occur because of permeability of the bag to diffusible gases in the bowel; this complication may be prevented by flushing the bag with carbon-dioxide before attachment to the tube.[336] The complications of intubation include sinusitis, laryngeal obstruction, esophageal stricture, knotting of the tube, rupture of a hollow viscus, rupture of esophageal varices and inability to withdraw a balloon-tipped tube because of occlusion of the air passage to the bag; breakage of the mercury-filled bag is a frequent occurrence but is without ill effects.[337]

*Massive Resection.*—A report is made of the removal of 19 feet 3 inches (586.7 cm.) of gangrenous jejunum and ileum (approximately 87 per cent of the small intestine) from a 22 year old soldier; the pathologic diagnosis was hemorrhagic necrosis of the small intestine.[338] Examination four and a half years later revealed an asymptomatic person with normal appetite and weight and satisfactory bowel function. In another patient, after resection of approximately 72 per cent of the small intestine, the nutritional state has been maintained satisfactorily for twelve months.[339]

No striking difference was observed in the degree of utilization of natural foods as compared to a synthetic diet in a patient with only 45 cm. of small intestine remaining.[340] Absorption tests revealed greater impairment of function than did nutritional balance studies.

*Vascular Lesions.*—Two patients, one with rapidly progressing hypertensive vascular disease and the other with polyarteritis nodosa, presented a clinical picture of predominantly intestinal disease.[341] The first patient had a short history of abdominal pain and bloody diarrhea, the second a more prolonged history of anemia and steatorrhea. The

335. Merendino, K. A., and Phelan, J. A.: A New, Safe, Simple Apparatus for Obtaining Negative Suction for the Patient with an Indwelling Gastrointestinal Tube, Surgery **25**:576, 1949.

336. Lewis, A. E., and Leff, W.: Gaseous Distention of the Latex Bag in the Use of the Single Lumen Intestinal Tube, Surgery **24**:1014, 1948.

337. Chaffee, J. S.: Complications of Gastrointestinal Intubation, Ann. Surg. **130**:113, 1949.

338. Gosse, M.: Massive Intestinal Resection, Mil. Surg. **103**:282, 1948.

339. Finley, R. K., and Joyce, R. P.: Volvulus of the Small Intestine Requiring Massive Resection, Am. J. Surg. **77**:643, 1949.

340. Althausen, T. L.; Uyeyama, K., and Simpson, R. G.: Digestion and Absorption After Massive Resection of the Small Intestine: I. Utilization of Food from a "Natural" Versus a "Synthetic" Diet and Comparison of Intestinal Absorption Tests with Nutritional Balance Studies in a Patient with Only 45 Cm. of Small Intestine, Gastroenterology **12**:795, 1949.

341. De Navasquez, S., and French, E. B.: Intestinal Ulceration Due to Arterial Necrosis (Malignant Hypertension and Periarteritis Nodosa), Guy's Hosp. Rep. **96**:85, 1947.

most striking pathologic finding in both instances was the presence of extensive ulceration due to necrotizing arteritis of the small intestine. The histologic appearances of the arterial lesions in the 2 patients were similar. In the patient with polyarteritis nodosa there was also complete disorganization of the mesenteric lymph nodes, which were the seat of extensive ischemic necrosis and replacement fibrosis; this, together with the ulcerative destruction of the intestinal mucosa, was the cause of the spruelike syndrome which had been present during life. Another interesting feature of this case was the persistent lymphopenia (25 to 1,250 lymphocytes per cubic millimeter) accounted for at necropsy by the observation of extensive ischemic necrosis of the splenic lymphoid tissue and by the destruction of mesenteric lymph nodes. Involvement of the abdominal viscera was noted at autopsy in 21 of 30 patients with periarteritis nodosa; symptoms referable to the gastrointestinal tract, chiefly abdominal pain, were present in 23.[342]

*Mesenteric Occlusion.*—The mortality of mesenteric vascular occlusion is high; the unsolved problem is diagnosis.[343] Successfully treated patients are described.[344]

*Malignant Tumors.*—The distribution of malignant growths of the small bowel is described.[345]

### PARASITIC AND DIARRHEAL DISEASES

*Epidemic Gastroenteritis.*—A filtrable agent, with the characteristics of a virus, recently isolated from the feces of infants with diarrhea, regularly reproduced the same disease in calves. The virus may be the cause of epidemic diarrhea of the newborn. Light and Hodes [346] recovered identical or closely related strains of virus from four separate epidemics in Washington, D. C., and Baltimore hospitals; in none of the epidemics were known pathogenic bacteria isolated.

The mortality rate was 50.6 per cent among 207 children with epidemic gastroenteritis in Aberdeen, Scotland,[347] and 40 per cent among

342. Wold, L. E., and Baggenstoss, A. H.: Gastrointestinal Lesions in Periarteritis Nodosa, Proc. Staff Meet., Mayo Clin. **24**:28, 1949.

343. Boyce, F. F.: The Unsolved Diagnostic Problem of Mesenteric Vascular Occlusion, South. Surgeon **14**:486, 1948.

344. Benjamin, D.: Mesenteric Thrombosis, Am. J. Surg. **76**:338, 1948. Dempsey, W. S., and Jones, T. E.: Venous Mesenteric Thrombosis, Cleveland Clin. Quart. **15**:140, 1948.

345. Maxwell, E. A.; Crile, G., Jr., and Dinsmore, R. S.: Malignant Tumors of the Small Intestine, S. Clin. North America **28**:1149, 1948. Likely, D. S.; Lisa, J. R.; Stitch, M. H., and Stein, H. D.: Primary Malignant Disease of the Small Bowel, Arch. Int. Med. **82**:206 (Aug.) 1948.

346. Light, J. S., and Hodes, H. L.: Isolation from Cases of Infantile Diarrhea of a Filtrable Agent Causing Diarrhea in Calves, J. Exper. Med. **90**:113, 1949.

347. Giles, C.; Sangster, G., and Smith, J.: Epidemic Gastro-Enteritis of Infants in Aberdeen During 1947, Arch. Dis. Childhood **24**:45, 1949.

384 infants in Brisbane, Australia.[348] Salmonella bovis-morbificans (Salmonella morbificans) was identified in half the entire series and in most of the fatal cases. Jaundice is an uncommon but well recognized complication of gastroenteritis[349]; histologic examination of the liver discloses necrosis of cells or accumulations of fat.

In the control and prevention of gastroenteritis among infants the following measures are emphasized: (*a*) awareness of the problem (*b*) institution of "infectious disease" technic for all personnel visiting gastroenteritis wards; (*c*) careful ward hygiene with efficient disposal of contaminated material, and (*d*) sterilization of food in completely covered units before being sent to the wards.[350] Various writers[351] discuss therapy, with particular emphasis on the correction of fluid and electrolyte imbalance. Streptomycin was given by mouth (2 Gm. daily) to 30 patients with infantile gastroenteritis; its effects were most striking in those with the critically acute illness, in those with recurrent diarrhea and vomiting and in those with neonatal gastroenteritis.[352] Goettsch and his associates[353] also stress the value of streptomycin. Administration of arobon,[®] prepared from carob bean flour and characterized by adsorptive and mild astringent properties, reduced the number of stools but did not cure the infection or prevent relapse.[354]

*Salmonella Infections.*—Four species of cockroach infected with five species of Salmonella excreted viable Salmonella in the feces for periods up to forty days, leading the authors to believe that cockroaches might act as vectors or temporary reservoirs of Salmonella infections.[355]

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348. Stable, G., and Philpott, I. G.: An Epidemic of Gastro-Enteritis in Infants, with Special Reference to Treatment, M. J. Australia **2**:63, 1948.

349. Schlesinger, B.; Payne, W. W., and Burnard, E. D.: Liver Damage in Gastro-Enteritis, Arch. Dis. Childhood **24**:15, 1949.

350. Mackerras, M. J., and Mackerras, I. M.: Prevention of Gastroenteritis in Infants, M. J. Australia **1**:477, 1949.

351. Lichtenstein, A.: Epidemic Diarrhea of the Newborn, Nord. med. **41**:1, 1949. O'Keefe, E. S.: Enteral Treatment of Diarrhea in Infancy, Including Epidemic Diarrhea of the Newborn, Am. J. Dis. Child. **76**:616 (Dec.) 1948. Davies, J.; Osborn, J.; Schwartz, R.; Ward, R. S., and Whittemore, J.: Dehydration in Infantile Diarrhea, M. Clin. North America **33**:851, 1949. Alexander, M. B.: Infantile Diarrhea and Vomiting: A Review of 456 Infants Treated in a Hospital Unit for Enteritis, Brit. M. J. **2**:973, 1948.

352. James, U., and Kramer, R. H.: Infantile Gastroenteritis Treated with Streptomycin by Mouth, Lancet **2**:555, 1948.

353. Goettsch, E.; Cobley, G., and Mulloy, M.: Treatment of Infantile Diarrhea with Streptomycin and Oral Amigen Mixture, Pediatrics **2**:1, 1948.

354. Beynon, D.: Arobon in the Treatment of Infantile Gastro-Enteritis: A Clinical Trial, Arch. Dis. Childhood **24**:41, 1949.

355. Mackerras, I. M., and Pope, P.: Experimental Salmonella Infections in Australian Cockroaches, Australian J. Exper. Biol. & M. Sc. **26**:465, 1948.

One hundred and eleven serologic types of Salmonella from 12,331 cultures derived from 7,365 outbreaks of disease and from asymptomatic carriers in man and animals are described.[356]

Massive doses of penicillin and sulfathiazole were given to patients known to be regular excreters of Salmonella typhi (Salmonella typhosa); though up to 40,000,000 units of penicillin and 12 Gm. of sulfathiazole daily were administered, there were only 3 apparent successes in ridding the patients of the organisms.[357]

*Bacillary Dysentery.*—The susceptibility of shigellae to a small group of antibiotic-producing E. coli strains is related to type specificity.[358] A survey of persons in a New York state institution for the presence of fecal lactose-fermenting organisms antagonistic against a strain of Shigella paradysenteriae Flexner type III revealed that 11.7 per cent of 2,648 strains were active and that 30 per cent of 287 persons harbored such organisms.[359]

Sixty children, aged 15 to 18, were given subcutaneous injections of polyvalent Shigella vaccines; vaccines standardized so as not to produce severe local and systemic toxic reactions stimulated increases in the protective power of serums which persisted for eighteen to fifty-two weeks.[360] Three booster injections of pentavalent Shigella vaccine seventy-eight weeks after primary vaccination stimulated significant increases in protective power in the pooled serum of girls for the component Shigella against which the protective power had decreased to insignificant levels. These increases persisted at least six weeks.[361] No significant increases appeared for homologous Shigella, for which there was still a significant level at the time of the booster injection.

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356. Edwards, P. R.; Brunner, D. W., and Moran, A. B.: Further Studies on the Occurrence and Distribution of Salmonella Types in the United States, J. Infect. Dis. **83**:220, 1948.

357. Fry, R. M.; Jones, R. E.; Moore, B.; Parker, M. T., and Thomson, S.: Treatment of Typhoid Carriers with Penicillin and Sulphathiazole, Brit. M. J. **2**:295, 1948.

358. Halbert, S. P., and Gravatt, M.: The Relation of Shigella Type-Specificity and Susceptibility to Antibiotic-Producing Strains of Escherichia Coli, J. Immunol. **61**:271, 1949.

359. Halbert, S. P.: The Relation of Antagonistic Coliform Organisms to Shigella Infections, J. Immunol. **60**:23, 1948.

360. Cooper, M. L.; Tepper, J., and Keller, H. M.: Studies in Dysentery Vaccination: VI. Primary Vaccination of Children with Polyvalent Vaccines of Shigella, J. Immunol. **61**:209, 1949.

361. Cooper, M. L.; Tepper, J., and Keller, H. M.: Studies in Dysentery Vaccination: VII. Response of Children to Booster Injections of Shigella Vaccines, J. Immunol. **61**:221, 1949.

In an outbreak of S. paradysenteriae infection aboard a ship, control subjects seemed to do as well as those treated with sulfadiazine; there were no deaths; and the disease in general was mild.[362]

A severe typhoid-like infection was attributed to a paracolon bacillus with Shigella antigens.[363] The organism was isolated repeatedly from the feces during the acute illness, and the infection was successfully treated with streptomycin parenterally. The serum agglutination titer for the organism rose after the acute illness.

*Typhoid.*—The incidence of typhoid among children of Kweichow, China, was 2.8 per cent; the mortality rate in children under the age of 12 was 3.2 per cent.[364] Treatment was supportive; sulfonamide therapy was not beneficial. Administration of penicillin and sulfathiazole to 8 chronic typhoid carriers caused the organisms to disappear, but they reappeared in all instances when treatment was discontinued.[365]

*Parasites.*—Specimens of pinworm ova are easily obtained with anal swabs of transparent cellulose tape.[366] A saline-aerosol-ether-xylene technic for concentrating helminth ova is advocated.[367]

A test antigen prepared from clean filariform larvae of Strongyloides cultured from the feces of the chimpanzee, in a dilution of 1:100, produced 23 positive intradermal reactions and 25 positive reactions to precipitin tests in 25 chronic cases of human strongyloidiasis. It is not known how long after cure the intradermal reaction will remain positive, although it is likely that the positive reaction to the precipitin test indicates the presence of specific antibodies.[368] Trichostrongylus infection in man is unusual and may be confused with hookworm; treatment with the usual anthelmintics is ineffectual.[369]

*Amebiasis.*—The incidence of amebiasis was 17 per cent among patients and personnel in a Memphis metropolitan hospital; the greatest

362. Williamson, R.; Fuller, R.; Martin, J. J., and Tuchewicz, H.: Bacillary Dysentery, U. S. Nav. M. Bull. **48**:818, 1948.

363. Bloch, L.; Milzer, A., and Nerdeman, E.: Typhoid-like Infection Due to Paracolon Bacillus, Gastroenterology **12**:509, 1949.

364. Kao, Y. E.: A Study on Typhoid Fever in Children in Kweichow: An Analysis of 126 Cases, Chinese M. J. **66**:391, 1948.

365. Korns, R. F., and Trussell, R. E.: Treatment of the Typhoid Carrier State, J. Lab. & Clin. Med. **33**:1150, 1948.

366. Beaver, P. C.: Methods of Pinworm Diagnosis, Am. J. Trop. Med. **29**:577, 1949.

367. Loughlin, E. H., and Spitz, S. H.: Diagnosis of Helminthiasis, J. A. M. A. **139**:997 (April 9) 1949.

368. Brannon, M. J. C., and Faust, E. C.: Preparation and Testing of a Specific Antigen for Diagnosis of Human Strongyloidiasis, Am. J. Trop. Med. **29**:229, 1949.

369. Evander, L. C., and Doyle, W. M.: Trichostrongylus Infections in Human Being: Need of Differentiation from Hookworm, J. Lab. & Clin. Med. **33**:869, 1948.

number of cases was among housewives and food handlers.[370] The importance of secondary infection associated with chronic amebic colitis is emphasized.[371]

In Durban, South Africa, three different racial populations live together. In the native African there is a high incidence of an acute, fulminating, rapidly fatal amebic dysentery. This form of the disease is not seen in either the European or the Indian inhabitants of the area. The three races differ in regard to diet and, to a certain extent, in their conditions of hygiene. However, the difference in virulence does not appear closely attributable to racial susceptibility, vitamin deficiency or the poor hygiene.[372]

Melarsen® oxide (50 mg. per kilogram of body weight), a pentavalent arsenical, oxyphenarsine (mapharsen®) hydrochloride U. S. P. (10 mg. per kilogram of body weight) and carbarsone U. S. P. (7.5 mg. per kilogram of body weight) proved effective against natural infections of Endamoeba histolytica in Macaca mulatta, when administered daily for ten days.[373]

Dogs maintained on a fish diet were highly susceptible to infection with a human strain of E. histolytica.[374] In the treatment of this experimental infection, emetine hydrochloride, carbarsone, chiniofon, diiodohydroxyquinoline and amodiaquin (7-chloro-4-[3-diethylamino-methyl-4-hydroxyanilino] quinoline) exerted antiamebic action. Cures were obtained with carbarsone, chiniofon and diiodohydroxyquinoline, but not with emetine or amodiaquin. Chloroquine diphosphate, sodium penicillin G, streptomycin, sulfadiazine and succinylsulfathiazole were ineffective. Bismuthoxy p-N-glycolylarsanilate was given orally in doses of 0.5 Gm. three times daily for ten days to patients with E. histolytica in the feces; all were promptly cleared of amebiasis.[375]

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370. Anderson, H. H.; Johnstone, H. G.; Packer, H.; Young, J. D.; Callison, M. K.; Hambly, A. S.; Anderson, J., and Reed, R. K.: Incidence and Control of Amebiasis and Other Intestinal Protozoan Infections in a Memphis Hospital, Am. J. Trop. Med. **28**:373, 1948.

371. Beemer, A. M.; Samuel, E., and Shedrow, A.: The Secondary Infection in Chronic Amoebic Colitis: A Clinicopathological and a Radiological Study, South African M. J. **22**:612, 1948.

372. Elsdon-Dew, R.: Endemic Fulminating Amebic Dysentery, Am. J. Trop. Med. **29**:337, 1949.

373. Kessel, J. F., and Kaplan, F.: Effect of Certain Arsenicals on Natural Infections of Endamoeba Histolytica and Endamoeba Polecki in Macaca Mulatta, Am. J. Trop. Med. **29**:319, 1949.

374. Thompson, P. E., and Lilligren, B. L.: Chemotherapy of Experimental Endamoeba Histolytica Infection in Dogs, Am. J. Trop. Med. **29**:323, 1949.

375. Dennis, E. W.; Berberian, D. A., and Hansen, S. S.: Amoebicidal Activity of Bismuthoxy p-N-Glycolyl-Arsanilate and 7-Iodo-4-(1-Methyl-4-Diethylamino Butylamino) Quinoline Diphosphate, Am. J. Trop. Med. **29**:683, 1949.

Chloroquine, an antimalarial compound, proved to be effective in the treatment of 8 patients with amebic hepatitis.[376] It was necessary in most cases to give diiodohydroxyquinoline (diodoquin®) or a similar drug to clear the feces of ameba. The successful treatment of 11 patients with amebiasis with the oral administration of aureomycin is reported by McVay and his associates[377]; in vitro studies indicated a decided amebicidal action of aureomycin.

*Schistosomiasis.*—The most important tropical diseases occurring in veterans are amebiasis and schistosomiasis; examination of warm purged stools for amebas and special concentration methods for Schistosoma eggs are required for diagnosis.[378] The importance of rectal biopsy in the diagnosis of schistosomiasis is stressed; in 50 unselected cases 27 were diagnosed by rectal biopsy and only 2 by the rectal scraper method.[379] Apparently the proctosigmoidoscopic findings are not sufficiently characteristic to permit a definite diagnosis on the basis of the gross appearance.[380] Kikuth and Gonnert[381] investigated the therapeutic effects of the miracils,® compounds belonging to the xanthone and thioxanthone class, in mouse and monkey schistosomiasis; miracil D® (1-methyl-4-beta-diethylaminoethylaminothioxanthine hydrochloride) may be the most suitable preparation for the treatment of human schistosomiasis.

*Lymphogranuloma Venereum.*—Seventy-four per cent of 31 patients with rectal strictures studied in Copenhagen, Denmark, had positive reactions to Frei tests.[382] Sulfonamides[383] and aureomycin[384] have been reported to give favorable therapeutic results.

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376. Conan, N. J.: The Treatment of Hepatic Amebiasis with Chloroquine, Am. J. Med. **6**:309, 1949.

377. McVay, L. V.; Laird, R. L., and Sprunt, D. H.: A Preliminary Report of the Successful Treatment of Amebiasis with Aureomycin, Science **109**:590, 1949.

378. Shookhoff, H. B.: Tropical Diseases of the Gastrointestinal Tract in Veterans, New York State J. Med. **48**:2133, 1948.

379. Meiser, C. V.; Ross, F.; Blain, O. B. E., and Edin, B.: The Rectal Diagnosis of Schistosomiasis, J. Trop. Med. **51**:91, 1948.

380. Podrígues da Silva, J.: Aspectos rectosigmoidoscópicos na esquistosomose mansoni, Rev. brasil de gastroenterol. **1**:117, 1949.

381. Kikuth, W., and Gonnert, R.: Experimental Studies on Therapy of Schistosomiasis, Ann. Trop. Med. **42**:256, 1948.

382. Hansen, A. G. A.: Frei Reaction: Important Diagnostic Aid in Rectal Strictures, Nord. med. **39**:1321, 1948.

383. Rake, G.: Chemotherapy of Lymphogranuloma Venereum, Am. J. Trop. Med. **28**:555, 1948.

384. Wright, L. T.; Sanders, M.; Logan, M. A.; Prigot, A., and Hill, L. M.: Aureomycin: A New Antibiotic with Virucidal Properties; Preliminary Report on Successful Treatment in 25 Cases of Lymphogranuloma Venereum, J. A. M. A. **138**:408 (Oct. 9) 1948.

*Actinomycosis.*—Actinomycosis involving the terminal portion of the ileum and the ascending colon was successfully treated with streptomycin, 1 Gm. daily for thirty days.[385] Massive penicillin therapy is recommended for abdominal actinomycosis.[386]

APPENDIX

*Acute Appendicitis.*—Roentgenograms of appendixes removed surgically and at autopsy revealed the presence of calculi in one third of those with acute inflammation and in 2.7 per cent of those without disease.[387]

The mortality rate in 194 infants and children under 10 years of age with acute appendicitis was 9.9 per cent; the rate varied from 44 per cent in infants below 2 years of age to only 2.4 per cent in children aged 8 to 10 years.[388]

The most important aspect of the diagnosis of appendicitis during pregnancy is an accurate history.[389] In only 9 of 52 patients was spasm of the rectus muscle or of the abdominal wall present. Tenderness over McBurney's point was noted in only 27 patients. Many of the patients had normal leukocyte counts. The most important problem in differential diagnosis was the pain associated with the enlarging uterus in the early stage of pregnancy and the "lightning" pains at term. In 23 cases of acute appendicitis occurring in pregnant women and treated surgically, the rate of fetal loss was 39.1 per cent, due chiefly to spontaneous abortion and premature labor.[390]

Recent mortality figures are 8.7 per cent [391] and 6.84 per cent.[392] In a series of 375 surgically removed appendixes, oxyurids were present in 10.7 per cent; the incidence in children was 34.4 per cent.[393]

*Tumors.*—A detailed clinical and anatomic description is given of primary carcinoma of the appendix; the tendency of this growth to

385. Pemberton, H. S., and Hunter, W. R.: Intestinal Actinomycosis Treated with Streptomycin, Lancet **1**:1094, 1949.

386. Sanford, G. E., and Barnes, R. O.: Massive Penicillin Therapy in Abdominal Actinomycosis, Surgery **25**:711, 1949.

387. Felson, B.: Appendical Calculi, Surgery **25**:734, 1949.

388. Greene, J. J.: Acute Appendicitis in Infants and Children Under 10 Years of Age, Am. J. Surg. **77**:744, 1949.

389. Krieg, E. G. M.: Appendicitis Occurring During Pregnancy: Diagnostic Review of 200 Cases, Am. J. Obst. & Gynec. **57**:736, 1949.

390. Hoffman, E. S., and Suzuki, M.: A Comparative Study of Acute and Chronic Appendicitis in Pregnancy, West. J. Surg. **57**:150, 1949.

391. Griswold, M. L., and Goodspeed, W. K.: Factors in the Mortality of the Ruptured Appendix, Ann. Surg. **129**:260, 1949.

392. Huebner, R.: Treatment of Acute Appendicitis with Perforation, Am. J. Surg. **77**:223, 1949.

393. Chipps, H. D.: Oxyurids in the Appendix, Northwest Med. **47**:662, 1948.

metastasis is great and its size so small that it may easily be overlooked on macroscopic examination.[394]

*Appendices Epiploicae.*—Six cases of primary disease of the appendices epiploicae are reported; the clinical features were those of an acute abdominal emergency simulating appendicitis.[395]

COLON

*Proctoscopic Examination.*—A sigmoidoscope with both proximal and distal light sources, each of which can be operated independently, is described by Turell.[396]

Fifteen hundred patients who had no diarrhea, rectal bleeding, anal pain, pruritus, hemorrhoids or recent change in bowel habits were examined by proctoscope.[397] The results are compared with those obtained in 393 patients with rectal complaints. Five rectal cancers and 79 benign polyps were detected in the first group and 6 rectal cancers in the second group. The necessity for the routine use of the sigmoidoscope in every physical examination of adult patients is reemphasized.[398]

*Megacolon.*—Whitehouse and Kernohan [399] studied the myenteric plexus in 11 cases of congenital megacolon, in 5 cases of secondary megacolon and in a series of controls. The plexus was observed to be absent in the most distal part of the colon in all cases of congenital megacolon. In 60 per cent it also was absent in the lower part of the sigmoid. In 20 per cent the myenteric plexus was absent from the rectum into the upper part of the sigmoid and the descending colon.

Of 73 cases of idiopathic megacolon, 39 conformed to Hirschsprung's clinical pattern; a narrow distal segment of intestine was demonstrable roentgenographically in 34.[400] The absence of parasympathetic ganglions

394. Kubicki, S.: Primary Carcinoma of the Appendix, Polski tygodnik lek. **3**:1243, 1278 and 1315, 1948. Lesnick, G., and Miller, D.: Adenocarcinoma of the Appendix, Cancer **2**:18, 1949.

395. Mavinis, T. P., and Cheek, J. H.: Primary Inflammation of the Appendices Epiploicae, Ann. Surg. **129**:533, 1949.

396. Turell, R.: A Sigmoidoscope with Proximal and Distal Illumination, Surgery **25**:601, 1949.

397. Steele, H. H., and Brown, C. H.: Analysis of 1500 "Routine" Proctosigmoidoscopic Examinations, Gastroenterology **12**:419, 1949.

398. Swinton, N. W.; Hare, H. F., and Meissner, W. A.: Diagnosis of Cancer of the Large Bowel, J. A. M. A. **140**:463 (June 4) 1949. Young, V. T.: Examination of the Lower Bowel, S. Clin. North America **29**:415, 1949. Evans, O. T.: The Proctoscopic Examination in Detecting Disease of the Rectum and Colon, Kentucky M. J. **47**:25, 1949.

399. Whitehouse, F. R., and Kernohan, J. W.: Myenteric Plexus in Congenital Megacolon: Study of 11 Cases, Arch. Int. Med. **92**:75 (July) 1948.

400. Bodian, M., and Stephens, F. D.: Hirschsprung's Disease and Idiopathic Megacolon, Lancet **1**:6, 1949.

in 15 cases studied histologically suggests uniform pathologic involvement due to lack of parasympathetic function; unopposed sympathetic activity accounts for the spasm of the distal segment. Resection of the diseased bowel is regarded as the treatment of choice.[401]

*Volvulus.*—Volvulus of the cecum is described.[402]

*Diverticulosis and Diverticulitis.*—The symptoms in 726 cases of uncomplicated diverticulosis of the colon were similar to those of irritable colon; cancer of the gastrointestinal tract was demonstrated in 3.5 per cent.[403] A clinical study of 205 ambulatory patients with diverticulosis of the colon indicated that diverticulosis does not produce clinical symptoms; diverticulitis occurred in 23 patients (11.2 per cent); carcinoma was present concomitantly in 2 patients.[404]

*Gas.*—A procedure for the quantitative collection and analysis of human colonic flatus is described.[405] The average output of gas by 45 normal subjects was 1.47 ml. per minute. Ingestion of brussel sprouts raised the gas output to 2.34 ml. per minute, most of the increased gas being nitrogen. Lactose and milk ingestion did not increase the output of gas. In patients with the "colitis syndrome" without organic pathologic changes and in patients with cardiac failure the output was not increased.

*Foreign Bodies.*—Twenty-four patients with foreign bodies in the colon and rectum are described.[406]

*Irradiation Proctitis.*—Sufficient irradiation to effect a cure of extrarectal pelvic cancer cannot be applied without risk of damage to the intestine. Histologic lesions suggesting irradiation effect on bowel tissue are hyaline change in the connective tissue, abnormal fibroblasts, telangiectasis, hypertrophy of the internal layers of the blood vessels, changes in the muscular tissue and epithelial and mucosal changes.[407]

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401. Dixon, C. F., and Judd, D. B.: The Surgical Treatment of Congenital Megacolon, S. Clin. North America **28**:889, 1948. Yeazell, L. A., and Bell, H. G.: Results of Medical and Surgical Management in 10 Cases of Congenital Megacolon, California Med. **70**:398, 1949.

402. McGraw, J. P.; Kremen, A. J., and Rigler, L. G.: The Roentgen Diagnosis of Volvulus of the Cecum, Surgery **24**:793, 1948. Dixon, C. J., and Meyer, A. C.: Volvulus of the Cecum, S. Clin. North America **28**:953, 1948. Palmer, J. D.: Volvulus of the Caecum, Canad. M. A. J. **60**:486, 1949.

403. Goodwin, F. H., and Collins, E. N.: Diverticulosis of the Colon, Cleveland Clin. Quart. **15**:194, 1948.

404. Feldman, M., and Morrison, S.: A Clinical Evaluation of Diverticulosis of the Colon, Am. J. Digest. Dis. **16**:126, 1949.

405. Kirk, E.: The Quantity and Composition of Human Colonic Flatus, Gastroenterology **12**:782, 1949.

406. ReBell, F. G.: The Problem of Foreign Bodies in the Colon and Rectum, Am. J. Surg. **76**:678, 1948.

407. Craig, M. S., Jr., and Buie, L. A.: Factitial (Irradiation) Proctitis, Surgery **25**:472, 1949. Maas, J. M.: Intestinal Changes Secondary to Irradiation of Pelvic Malignancies, Am. J. Obst. & Gynec. **56**:249, 1948.

*Experimental Studies of Colonic Function in Man.*—In approximately half of 45 experiments on 39 subjects without clinical disorder of the colon, definite increases in the contractile state of the colon were observed when the subjects were subjected to stress of the type regarded as a threat to security.[408] The motility of the colon was studied by proctoscopy or by means of inlying balloons in 39 patients with spastic constipation or colonic pain.[409] The results were similar to those obtained in persons with no clinical disorder of the colon and suggested that the fundamental abnormality in the patient with spastic constipation lies not in the behavior of his colon but in his susceptibility to stress-producing life situations. Six patients are presented to demonstrate that diarrhea was a psychosomatic reaction aimed at solving a specific unconscious emotional conflict.[410]

*Effect of Methacholine on Colon of Dogs.*—The prolonged daily administration of methacholine in dogs may produce a series of pathologic changes in the large bowel, ranging from severe hyperemia and interstitial mucosal hemorrhages to erosion and ulcer formation.[411] Bloody diarrhea appeared after almost every injection of methacholine, and the intestine at autopsy presented a hemorrhagic appearance.

*Ulcerative Colitis.*—The clinical course of chronic ulcerative colitis was studied on the basis of a representative series of 100 patients for whom complete follow-up data were available.[412] The mortality was highest among young patients with severe symptoms during the first one or two years of the disease. Complete "cure" was recorded after medical management in 6 persons; 47 were maintained in satisfactory health, and 19, although not responding dramatically, were not seriously incapacitated. Surgical treatment restored 14 of 19 patients to satisfactory health; 5 died. There were 9 medical deaths, 6 occurring prior to 1942. A similar study in Prague, Czechoslovakia, and Chicago indicated that the disease follows a similar pattern in Czechoslovakia and the United States.[413]

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408. Almy, T. P.; Kern, F., Jr., and Tulin, M.: Alterations in Colonic Function in Man Under Stress: II. Experimental Production of Sigmoid Spasm in Healthy Persons, Gastroenterology **12**:425, 1949.

409. Almy, T. P.; Hinkle, L. E., Jr.; Berle, B., and Kern, F., Jr.: Alterations in Colonic Function in Man Under Stress: III. Experimental Production of Sigmoid Spasm in Patients with Spastic Constipation, Gastroenterology **12**:437, 1949.

410. Sperling, M.: Diarrhea: A Specific Somatic Equivalent of an Unconscious Emotional Conflict, Psychosom. Med. **10**:331, 1948.

411. Wener, J.; Hoff, H. E., and Simon, M. A.: Production of Ulcerative Colitis in Dogs by the Prolonged Administration of Mecholyl, Gastroenterology **12**:637, 1949.

412. Kirsner, J. B.; Palmer, W. L.; Maimon, S. N., and Ricketts, W. E.: Clinical Course of Chronic Nonspecific Ulcerative Colitis, J. A. M. A. **137**:922 (July 10) 1948.

413. Maratka, Z., and Spellberg, M. A.: Observations on the Clinical Course of Non-Specific Ulcerative Colitis, Gastroenterology **12**:79, 1949.

The mean fecal lysozyme content in patients with chronic ulcerative colitis is twenty-seven times greater than normal and the mean twenty-four-hour output one hundred and sixty-eight times greater than normal.[414] After purging, the twenty-four hour output of the enzyme in healthy persons is 6.7 times larger than normal, but the concentration of the enzyme decreases by approximately one third. The lysozyme content of the feces in persons with regional enteritis is 6.1 times that of normal persons. The colonic mucosa of patients with ulcerative colitis contains 8.5 times more lysozyme than the normal mucosa. Experimental ulceration in the colon of the dog was produced by the oral administration of lysozyme. Inactivation of lysozyme by paranitrosulfazole (nisulfazole®) and anionic detergents occurs in gastric juice and tears but not in ulcerative colitis stools. Perhaps the proteins in the ulcerative colitis stool compete with lysozyme for the inhibitors.

The concentration of lysozyme increases transiently among normal subjects and subjects with diarrhea, but without ulceration, in conjunction with general reactions of humiliation with anxiety, resentment and guilt.[415] In patients with ulcerative colitis, pronounced and sustained elevations of lysozyme were observed in such situations. These periods were characterized by feelings of intense anger and hostility which were unexpressed and repressed with varying degrees of completeness. Lysozyme concentration in bowel secretions is highly relevant to the occurrence of ulceration. Variations in the production of lysozyme correspond to variations in the state of security of the organism as a whole. Under experimental conditions various materials were observed to be active inhibitors of lysozyme.[416]

[These observations concerning the relationship of lysozyme to ulcerative colitis are of considerable interest. The reviewers have likewise noted a pronounced increase in the output of lysozyme in the feces of patients with active ulcerative colitis. However, an unequivocal cause and effect relationship does not appear to have been established. The possibility remains that the rise in lysozyme titer represents a phenomenon secondary to inflammation, ulceration or necrosis of tissue. Serial determinations of the lysozyme content of the feces in dogs, indeed, suggest that such a sequence of events may take place.]

414. Meyer, K.; Gellhorn, A.; Prudden, J. F.; Lehman, W. L., and Steinberg, A.: Lysozyme Activity in Ulcerative Alimentary Disease: II. Lysozyme Activity in Chronic Ulcerative Colitis, Am. J. Med. **5**:496, 1948; Rev. Gastroenterol. **16**: 476, 1949.

415. Grace, W. J.; Seton, P. H.; Wolf, S., and Wolff, H. G.: Studies of the Human Colon: I. Variations in Concentration of Lysozyme with Life Situation and Emotional State, Am. J. M. Sc. **217**:241, 1949.

416. Moss, J. N., and Martin, G. J.: The Inhibition of Lysozyme Activity, Am. J. Digest. Dis. **15**:412, 1949.

Investigation of ulcer formation in 120 surgical and 60 autopsied patients with ulcerative colitis indicated that local vasculitis was responsible in 11 per cent and abscesses of mucosal crypts in 39 per cent; the ulcers were of indeterminate origin in 50 per cent.[417] In a study of ileac involvement in ulcerative colitis, the length of the diseased segment varied from 4 to 45 cm. In 7 patients solitary ulcers were present, sometimes extending throughout the length of the small bowel. Twenty-two patients showed diffuse ulceration. Perforation of the ulceration of the ileum with generalized peritonitis was a serious complication, occurring in 17 per cent.[418] Visualization with thorium dioxide offers a technically satisfactory additional means of examining the defunctionalized large bowel.[419]

In an investigation of 134 children the disease was considered to be infectious in origin.[420] Cocci and hemolytic types of colon bacilli were preponderant in the feces in the acute stages. Good therapeutic results were obtained with salazopyrin (salicylazosulfapyridine). Of 34 women with ulcerative colitis undergoing 50 pregnancies, the pregnancy was not adversely affected in 43.[421]

Some degree of hepatic insufficiency was noted in approximately 50 per cent of 70 patients with chronic ulcerative colitis.[422] Histologic evidence of hepatic disease, chiefly degenerative fatty infiltration, was observed in 11 of 17 patients studied at necropsy. In pyoderma gangrenosum complicating ulcerative colitis, no pathognomonic bacterial flora was found; treatment with sulfonamides and penicillin was not of value; the skin lesions healed as the ulcerative colitis was controlled.[423] Dramatic healing of pyoderma gangrenosum is described following treatment with aureomycin.[424]

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417. Warren, S., and Sommers, S. C.: Pathogenesis of Ulcerative Colitis, Am. J. Path. **25**:657, 1949.

418. McCready, F. J.; Bargen, J. A.; Docherty, M. B., and Waugh, J. M.: Involvement of the Ileum in Chronic Ulcerative Colitis, New England J. Med. **240**:119, 1949.

419. Shull, H. J.; Schulz, M. D., and Jones, C. M.: Roentgen Examination of the Defunctioned Colon after Ileostomy, with Special Reference to the Safety and Practical Value of Thorium Dioxide as a Contrast Medium, Gastroenterology **12**:1, 1949.

420. Lagercrantz, R.: Ulcerative Colitis in Children, Nord. med. **41**:258, 1949.

421. Felsen, J., and Wolarsky, W.: Chronic Ulcerative Colitis and Pregnancy, Am. J. Obst. & Gynec. **56**:751, 1948.

422. Pollard, H. M., and Block, M.: Association of Hepatic Insufficiency with Chronic Ulcerative Colitis, Arch. Int. Med. **82**:159 (Aug.) 1948.

423. Ricketts, W. E.; Kirsner, J. B., and Rothman, S.: Pyoderma Gangrenosum in Chronic Non-Specific Ulcerative Colitis, Am. J. Med. **5**:69, 1948.

424. Wright, L. T., and Strax, S.: Pyoderma Gangrenosum in Chronic Non-Specific Ulcerative Colitis Treated with Aureomycin, Harlem Hosp. Bull. **1**:99, 1948.

Bargen [425] comments on the similarity of ulcerative colitis and rheumatic fever. Salazopyrin, a combination of salicylate and sulfapyridine, has been used in 8 cases with success. Salazopyrin was given to 124 patients during the period 1940 to 1944; 108 were regarded as greatly improved or actually cured.[426] "Medical" ileostomy is recommended.[427] In 2 patients a dramatic response was noted to medical treatment which included testosterone propionate parenterally.[428]

Sodium phthalylsulfacetimide is highly soluble, relatively nontoxic, and poorly absorbed from the intestine and diffuses into the bowel wall.[429] Improvement in 18 of 28 patients with ulcerative colitis was obtained after treatment with 9 Gm. of phthalylsulfacetimide daily for five days or repeated until clinical benefit was established.[430]

The conditions of 24 of 27 patients treated for one year or longer with 50 to 100 Gm. daily of extracts of hogs' small intestine are considered to have improved.[431] After a successful course of therapy, discontinuance of the preparation, substitution of a placebo or use of intestinal extracts prepared by a different method, resulted in a relapse; remissions occurred once more on resumption of treatment with an effective extract. The majority of 28 patients with chronic ulcerative colitis are reported to have improved after treatment with a preparation of desiccated, defatted hog duodenum for twelve to eighteen months.[432] Rowe [433] maintains that patients should be studied by elimination diets and pollen sensitivity tests to determine allergic factors and treatment then carried out accordingly.

[Ulcerative colitis obviously continues to present a therapeutic dilemma. The wide variety of drugs and regimens reportedly beneficial

425. Bargen, J. A.: Evaluation of the Newer Therapy of Ulcerative Colitis, South. M. J. **41**:646, 1948.

426. Svartz, N.: Traitement de la colite ulcéreuse par la salozopyrine, Semaine d. hôp. Paris **24**:1677, 1948.

427. Miller, T. G., and Machella, T. E.: Principles in the Management of Chronic Non-Specific Ulcerative Colitis, Am. J. M. Sc. **216**:425, 1948.

428. Brown, C. H., and Perry, J. H.: Medical Treatment for Acute Toxic Ulcerative Colitis, Cleveland Clin. Quart. **16**:126, 1949.

429. Lehr, D.: Experimental Evaluation of a New Gastrointestinal Antiseptic —Sodium Phthalylsulfacetimide, Gastroenterology **12**:648, 1949.

430. Heineken, T. S., and Seneca, H.: Phthalyl Sulfacetimide in Ulcerative Colitis, Rev. Gastroenterol. **15**:611, 1948.

431. Friedman, M. H. F., and Haskell, B. F.: Treatment of Non-Specific Ulcerative Colitis for One Year with Extracts of Intestinal Mucosa, Gastroenterology **11**:833, 1948.

432. Streicher, M. H.; Grossman, M. I., and Ivy, A. C.: Preliminary Report of a Clinical Trial of Orally Administered Hog Duodenum Powder in the Treatment of Chronic Ulcerative Colitis, Gastroenterology **12**:371, 1949.

433. Rowe, A. H.: Ulcerative Colitis: Allergic Aspects, California Med. **70**: 58, 1949.

in this disease clearly indicates that a consistently effective program of treatment, applicable to most cases, has not been developed. Sustained improvement has been observed in a significant number of patients without the use of "specific" antibiotics or extracts. The reviewers continue to be impressed with the importance of long-continued rest, maintenance of nutrition and intelligent, optimistic psychotherapy by the interested physician. They are of the opinion, furthermore, that the disease is commoner than has been apparent heretofore. Further careful studies of the pathogenesis and life history of the patient and the disease are urgently needed.]

One hundred and sixty-six patients (26 per cent of total patients treated) were subjected to ileostomy or colectomy for ulcerative colitis.[434] There were 37 operative deaths. Two thirds of these occurred in patients who had an emergency ileostomy. During 1945 and 1946, 75 patients were operated on with 3 deaths, a mortality of 4 per cent. The authors feel that surgical treatment is justified in all patients with ulcerative colitis that does not respond satisfactorily to medical treatment. Ileostomy, in most cases, must be followed by removal of the colon; a high proportion of patients with total colectomy are in excellent health.

In 149 patients with ulcerative colitis in whom ileostomy was the initial or only procedure, the mortality rate was 14.8 per cent; a colectomy subsequently was performed in 87 (68.5 per cent) of the survivors, with a fatality rate of 6.9 per cent.[435] The rectal stump was removed in 33, or 40.7 per cent, of those surviving colectomy, with a mortality of 3.3 per cent. Among 104 of those patients whose present status was determined, 84 per cent considered themselves in good health. Among 23 chronically ill patients with ulcerative colitis subjected to various surgical procedures, the postoperative mortality was 13 per cent and the subsequent mortality 8.7 per cent; 73.8 per cent were restored to health; the status of 4 per cent of the patients was unknown.[436]

Ten patients with advanced ulcerative colitis were treated with subtotal or total colectomy.[437] Six were considered cured; the condition of 1 was improved; 1 died after initial enterostomy; 1 died three months after colectomy from inanition and bronchopneumonia, and 1 died from acute obstruction two years after colectomy. Primary resection of the

434. Cattell, R. B., and Sachs, E., Jr.: Surgical Treatment of Ulcerative Colitis, J. A. M. A. **137**:929 (July 10) 1948.

435. McKittrick, L. S., and Moore, F. D.: Ulcerative Colitis, J. A. M. A. **139**:201 (Jan. 22) 1949.

436. Ault, G. W.: Surgical Treatment of Ulcerative Colitis, Arch. Surg. **58**:243 (March) 1949.

437. Devine, H., and Devine, J.: Subtotal Colectomy and Colectomy in Ulcerative Colitis, Brit. M. J. **2**:127, 1948.

colon with permanent ileostomy in 24 cases of ulcerative colitis was attended by no mortality and by less morbidity than with ileostomy alone.[438] The Dragstedt ileostomy covered with a skin graft is the most satisfactory method of avoiding the difficulties which often accompany the usual type of ileostomy.[439]

In a series of 25 patients with ulcerative colitis, 16 had been treated by vagotomy alone; 6 became free of symptoms; the condition of 4 was improved, that of 5 remained unimproved and that of 1 was worse.[440] Nine patients had undergone an ileostomy or some form of ileoproctostomy in addition to vagotomy; 4 became free of symptoms, 3 were improved, 1 remained unimproved and 1 became worse. Reduction in the vascular response of the mucosa to intense emotion and the relief of enteric spasm are regarded as among the factors contributing to the improvement. Bilateral subdiaphragmatic vagotomy was performed in 8 patients with chronic nonspecific ulcerative colitis; all are considered to have responded favorably to the procedure.[441] [The reviewers look on this procedure as a surgical type of psychotherapy, with results not dependent on the specific nerves sectioned.]

*Polyps and Other Tumors.*—Rats fed motor-lubricating oil displayed foci of colonic mucosal hyperplasia and one colonic adenocarcinoma.[442] In a second experiment the oil produced an adenomatous infiltrating mucosal lesion in the colons of 50 per cent of the animals.

Rectal polyps were observed at sigmoidoscopy in 18 of 1,014 apparently healthy women over 21 years of age; 11 tumors were benign, and 8 were malignant.[443] Kerr [444] found one or more polyps in 100 of 349 children with symptoms referable to the bowel. The pathogenesis of intestinal polyps is traced by Atwater.[445] Papillary adenomas of the

438. Miller, G. G.; Gardner, C. M., and Ripstein, C. B.: Primary Resection of the Colon in Ulcerative Colitis, Canad. M. A. J. **60**:584, 1949.

439. Sanders, G. B.: Experiences with the Dragstedt Skin-Covered Ileostomy, Arch. Surg. **57**:487 (Oct.) 1948.

440. Dennis, C.; Eddy, F. D.; Frykman, H. M.; McCarthy, A. M., and Westover, D.: The Response to Vagotomy in Idiopathic Ulcerative Colitis and Regional Enteritis, Ann. Surg. **128**:479, 1948.

441. Thorek, P.: Vagotomy for Chronic Non-Specific Ulcerative Colitis, J. Internat. Coll. Surgeons **11**:578, 1948.

442. Lushbaugh, C. C., and Hackett, A.: An Infiltrating Adenomatosis Lesion of the Colon of Rats Ingesting Motor Lubricating Oil (S. G. F. No. 1 Oil), J. Nat. Cancer Inst. **9**:159, 1948.

443. Ortmayer, M., and Connelly, M.: A Study of the Colon of Apparently Well Women, J. Nat. Cancer Inst. **9**:399, 1949.

444. Kerr, J. G.: Polyposis of the Colon in Children, Am. J. Surg. **76**:667, 1948.

445. Atwater, J. S.: Polyps of the Colon—Their Origin and Growth, J. M. A. Georgia **37**:251, 1948.

colon show a definite tendency to recur; 68.7 per cent contain areas of cytologic carcinoma; 39.5 per cent develop into invasive carcinoma.[446] On the basis of a review of 1,402 patients, Buie and his co-workers[447] conclude that fulguration is an effective method of treating colonic polyps within reach of the proctoscope, but great care must be used in selecting patients. Radical surgical treatment is indicated in large disseminated polypoid lesions. Cattell[448] reports a series of 78 colonic polyps removed by colotomy, with a mortality of 2.6 per cent; more than 50 per cent of polyps were found to occur in the distal part of the bowel within visualization of the sigmoidoscope. A suction funnel for grasping and manipulating rectal and rectosigmoid polyps is described.[449]

Features distinguishing polyposis of the colon as a disease entity are its tendency to occur in certain families, the diffuse involvement of the colon and the propensity of the lesions early to undergo malignant change.[450] Cure depends on its recognition and either total ablation of the large bowel or total colectomy and ileosigmoid anastomosis, combined with fulguration of polyps in the preserved segment.

Ten patients with family histories of diffuse polyposis of the colon are presented, including one family in which carcinoma or diffuse polyposis of the bowel had occurred in more than half the members.[451] Ileosigmoidostomy, followed by subtotal colectomy and fulguration of rectal polyps, was an acceptable form of treatment.[452]

Among 16 cases of lipoma of the colon, 9 were in the right portion.[453]

*Carcinoma.*—As emphasized repeatedly in the past, the index of suspicion of carcinoma of the large bowel is low; approximately 43 per cent of 95 patients with carcinoma had been treated for bowel conditions

446. Sunderland, D. A., and Binkley, G. E.: Papillary Adenomas of the Large Intestine, Cancer **1**:184, 1948.

447. Buie, L. A.; Smith, N. R.; Jackman, R. J., and Hill, J. R.: Polypoid Lesions of the Terminal Portion of the Colon, with Special Relationship to Fulguration, J. A. M. A. **139**:702 (March 12) 1949.

448. Cattell, R. B.: Surgical Treatment of Polyps of the Large Intestine, Am. J. Surg. **76**:733, 1948.

449. Morton, P. C.: Treatment of Rectal and Rectosigmoid Polyps: Funnel Tip Suction as Aid in Their Removal, J. A. M. A. **138**:1090 (Dec. 11) 1948.

450. Hoxworth, P. I., and Slaughter, D. P.: Polyposis (Adenomatosis) of the Colon, Surgery **24**:188, 1948.

451. Rankin, J. W., and Webb, J. G.: The Surgical Treatment of Polyposis of the Colon, South. Surgeon **14**:671, 1948.

452. Jones, T. E., and Turnbull, R. B., Jr.: Familial Polyposis of the Colon: Diagnosis and Treatment, S. Clin. North America **28**:1171, 1948. Skinner, H. L., and Smith, R. H.: Colectomy, Am. J. Surg. **77**:38, 1949.

453. Mayo, C. W.: Lipoma of the Colon, Proc. Staff Meet., Mayo Clin. **24**:9, 1949.

other than the neoplasm.[454] Of 38 patients with colloid adenocarcinoma in the perianal region, anus, rectum and sigmoid colon, 45 per cent were dead in less than a year after the diagnosis was made.[455] In 441 cases of malignant tumors of the colon and rectum the rate of resectability was 35 to 40 per cent for tumors of the rectum and rectosigmoid and 45 to 62 per cent for lesions proximal to this level.[456] A study of patients who underwent resection of the colon for carcinoma during the period 1907 to 1944 revealed multiple tumors in 3 per cent; the presence of multiple malignant neoplasms reflects the inherent susceptibility of some persons to cancer.[457]

A twelve year follow-up study of 142 patients with cancer of the large bowel in a moderate-sized general hospital discloses results decidedly poorer than those reported by large cancer centers and outstanding surgeons.[458] This study very likely reflects the status of management of and the outlook for intestinal cancer throughout the country more accurately than do the brilliant statistics reported by large medical centers. Hopkins and Tate [459] attribute the steady drop in operative mortality for cancer of the rectum to chemotherapy and better understanding of body chemistry. There is apparent cure of 81.2 per cent of patients without obvious metastases who did not die of other causes.

Three hundred and eighty-eight patients with carcinoma of the lower sigmoid and rectum treated by combined abdominoperineal resection were reviewed to determine significance of the level of the lesion in prognosis.[460] Patients with lesions within 5 or 6 cm. of the anal margin have a poorer prognosis than those with lesions at a level of 7 to 10 cm., while those with lesions above 11 cm. have an even better prognosis. Conservative resection is evaluated by Gray [461] and Muir.[462]

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454. McNealy, R. W., and Smith, D.: Unnecessary Rectal Operations Done in the Presence of Cancer of Large Bowel, Illinois M. J. **94**:315, 1948.

455. Hill, J. R., and Smith, N. D.: Colloid Adenocarcinoma Involving the Perianal Region, Anus, Rectum or Sigmoid Colon, Am. J. Surg. **76**:642, 1948.

456. Postlethwait, R. W.: Malignant Tumors of the Colon and Rectum, Ann. Surg. **129**:34, 1949.

457. Thomas, J. F.; Dockerty, M. B., and Waugh, J. M.: Multiple Primary Carcinomas of the Large Intestine, Cancer **1**:564, 1948.

458. Bleicher, J. E.: Cancer of the Colon and Rectum: A Twelve Year Survey of 142 Cases in a General Hospital, Cancer **2**:25, 1949.

459. Hopkins, F. S., and Tate, R. C.: Carcinoma of the Rectum, New England J. Med. **239**:501, 1948.

460. Waugh, J. M., and Kirklin, J. W.: The Importance of the Level of the Lesion in the Prognosis and Treatment of Carcinoma of the Rectum and Low Sigmoid Colon, Ann. Surg. **129**:22, 1949.

461. Gray, J.: Evaluation of Conservative Resection with End to End Anastomosis for Carcinoma of the Rectum and Lower Sigmoid Colon, Arch. Surg. **57**:361 (Sept.) 1948.

462. Muir, E. G.: Rectal Cancer and Preservation of Function, Brit. M. J. **2**:286, 1948.

Of 301 patients with carcinoma subjected to combined abdominoperineal resection, 121 survived five years.[463] Lymph node metastases were observed in the resected specimens from 42 of the survivors.

The five year survival rate in 37 cases of completely obstructing annular carcinoma of the descending colon and sigmoid in which resection was performed was 25.7 per cent, as compared with 51.7 per cent in cases in which nonobstructing lesions had been treated surgically.[464]

Therapy with roentgen rays generated at 1,000,000 volts plays a definite role in the treatment and management of carcinoma of the rectum.[465] Regression of the primary tumor is more certainly obtained in squamous cell carcinoma of the anal canal than in adenocarcinoma of the rectum. In both sites excellent palliation and prolongation of comfortable life can be expected in patients with advanced disease, provided the disease is confined to the pelvis. Although the figures for long term survival are small, they are better than those for alternative forms of roentgen therapy. The improvement in the effects of these radiations is due to the increased depth dose and to the greater accuracy, efficiency and ease of application.

### ANUS AND RECTUM

*Fecal Continence.*—Studies of the mechanism of fecal continence indicated that fecal material stimulates receptor units in the rectum which, through a reflex arc, relax the internal sphincter to permit evacuation.[466] The external sphincter responds to stimulation by reflex or voluntary contraction. The usual cause of sphincter incontinence is division of the external sphincter by surgical, puerperal or accidental injury; all other factors are neurologic in origin.

*Anal Spasm.*—Spasm and fibrosis of the anal sphincter are described in 21 patients.[467] The treatment advocated consists of anal dilatation with the patient under general anesthesia, followed by daily dilatation with finger or dilators.

*Pruritus—Hemorrhoids.*—Jenkins [468] reports good results with the administration of methylrosaniline chloride (gentian violet) orally and

463. Wilson, E.: Restorative Resections for Carcinoma of the Rectum, Australian & New Zealand J. Surg. **18**:224, 1949.

464. Nickel, D. F., and Dockerty, M. B.: The Five-Year Survival Rate in Cases of Completely Obstructing Annular Carcinoma of the Descending Colon and Sigmoid, Surg., Gynec. & Obst. **87**:519, 1948.

465. Williams, I. G.: Carcinoma of the Rectum and Anal Canal: Treatment with Very High Voltage X-Ray Therapy, Brit. J. Surg. **36**:376, 1949.

466. Gaston, E. A.: Physiology of Fecal Continence, Surg., Gynec. & Obst. **87**:280, 1948.

467. Newton, F. C., and Macgregor, C. A.: Spasm and Fibrosis of the Sphincter Ani Due to Reflex Action, New England J. Med. **239**:113, 1948.

468. Jenkins, J. T.: Pruritus Ani: A Study of Results with Gentian Violet in 210 Cases, Am. J. Surg. **76**:763, 1948.

locally in the treatment of pruritus ani. All patients with pruritus ani et vulvae were considered to have eczema.[469] About 85 per cent had had eczema in the skin distant from the perineum. Treatment consists of rest, sedation and relief of emotionally disturbing factors; roentgen therapy is of value but care must be exercised.

*Tuberculosis.*—Satisfactory results are reported in 27 cases of anorectal tuberculosis treated with streptomycin with and without surgical intervention.[470]

### MISCELLANEOUS GASTROINTESTINAL SUBJECTS

*Appetite.*—Sugar when tasted and ingested is capable of producing a decrease in olfactory acuity and of converting the sensation of appetite into one of satiety.[471] This effect did not occur from stimulation of taste organs alone or from ingestion of sugar without tasting it. Dextrose given intravenously did not decrease olfactory acuity or produce the sensation of satiety. Thus, the influence of sugar on olfactory acuity, appetite and satiety involves more than one gastrointestinal mechanism.

*Nutritional Problems.*—Gastrointestinal disease and reduced dietary intake constituted the chief predisposing causes in 67 per cent of a series of 200 cases of nutritional disorders.[472] No correlation was found between the fraction of thiamine excreted and the habitual thiamine intake.[473]

*Effect of Streptomycin on Fecal Flora.*—In the majority of cases administration of 2 Gm. of streptomycin by mouth per day will give virtually sterile cultures of the feces after forty-eight hours.[474] In cases of obstruction and in some cases of diarrhea, this response does not occur. Phthalylsulfathiazole given for a week prior to streptomycin prevented the development of streptomycin fastness. The oral administration of streptomycin decreased by 80 to 100 per cent the fecal bacterial counts in 4 patients prior to surgical treatment. The maximum effect was within

469. Hailey, H.: Pruritus Ani et Vulvae: Report of 520 Consecutive Patients with Eczema of the Anal and Vulval Regions, J. A. M. A. **139**:837 (March 26) 1949.

470. Koonty, E. R.: Streptomycin and Surgery in Anorectal Tuberculosis, S. Clin. North America **28**:1643, 1948.

471. Goetzel, F. R.; Goldschmidt, M.; Wheeler, P., and Stone, F.: Influence of Sugar upon Olfactory Acuity and upon the Sensation Complex of Appetite and Satiety, Gastroenterology **12**:252, 1949.

472. Sieve, B. F.: Vitamins and Hormones in Nutrition: IV. Gastro-Intestinal Disease and Reduced Dietary Intake, Am. J. Digest. Dis. **15**:275, 1948.

473. Laing, G.; Jones, F. W.; Anderson, D., and Beazell, J. M.: The Thiamine Excretion Test as a Measure of Dietary Adequacy, Gastroenterology **12**:450, 1949.

474. Morton, H. S., and Smith, F.: Preoperative Place of Streptomycin in Operations on the Bowel, Arch. Surg. **57**:520 (Oct.) 1948.

forty-eight hours.[475] Concomitantly, the prothrombin time increased, varying from 22 to 23 seconds (whole plasma method) and from 51.1 to 66.0 seconds (dilute plasma method). It is suggested that vitamin K be administered preoperatively and postoperatively when streptomycin is given orally as a chemotherapeutic agent.

Serial colony counts of three groups of fecal organisms, the coliform group, the streptococci and the clostridia, were made in 24 patients given streptomycin orally.[476] Half the specimens showed no response in the number of the coliform organisms; 87 per cent showed no significant response in number of streptococci; 39 per cent showed no significant reduction in the number of clostridia. The E. coli group rapidly developed resistance to streptomycin. It is concluded that the effect of orally administered streptomycin is unpredictable and unreliable and that its use is not to be recommended in preoperative preparation of surgical patients. Colon and aerogenes bacilli resistant to streptomycin appeared in the stools of patients with tuberculosis under streptomycin treatment; sensitive bacilli returned after cessation of therapy.[477] [The reviewers also have noted the development of strains of bacteria resistant to streptomycin shortly after the administration of this antibiotic; the duration of the resistant quality remains to be determined.] Pulaski and Baker [478] demonstrated that streptomycin in combination with penicillin and sulfadiazine was optimally bacteriostatic for gram-negative bacteria, and these drugs used in combination delayed the emergence of drug-fast cultures. These studies suggest that, in addition to the use of combinations of penicillin, streptomycin and the sulfonamides for treatment of mixed infections caused by several species of bacteria, such combinations may be useful for therapy in infections caused by a single etiologic agent.

*Peritonitis.*—Sulfonamides administered to dogs with experimentally induced peritonitis had no effect.[479] Doses of streptomycin that effec-

475. Herfort, R. A., and Standard, S.: Oral Streptomycin in Surgery of the Large Bowel: The Production of Secondary Hypoprothombinemia, Ann. Surg. **128**:987, 1948.

476. Lockwood, J. S.; Young, A. D.; Bouchelle, M.; Bryant, T. R., and Stajowski, A. J.: Appraisal of Oral Streptomycin as an Intestinal Antiseptic, with Observations on Rapid Development of Resistance of E. Coli to Streptomycin, Ann. Surg. **129**:14, 1949.

477. Hamburger, M.; Berman, J. R., and Fabrizio, A.: The Development of Streptomycin Resistant Bacteria in the Stools of Patients Treated for Tuberculosis, J. Lab. & Clin. Med. **33**:1460, 1948.

478. Pulaski, E. J., and Baker, H. J.: In Vitro Effects on Gram-Negative Bacteria of Streptomycin Combined with Penicillin and/or Sulfadiazine, J. Lab & Clin. Med. **34**:186, 1949.

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tively controlled the organisms in the peritoneal cavity caused death from the toxic effect of the drug. Commercially available penicillin, 500,000 units alone or combined with 2.4 Gm. of streptomycin given intramuscularly at four hour intervals, was effective in preventing deaths of 10 dogs. A dosage of 100,000 units of 25 per cent penicillin X intramuscularly prevented death in 9 of 10 animals. Comparison of 598 cases of peritonitis with and 685 cases without chemotherapy revealed a reduction in mortality of about 60 per cent among those with chemotherapy; the combined parenteral administration of streptomycin, penicillin and sulfadiazine appeared to be more effective than any of the drugs given singly.[480] Five patients with peritonitis were treated successfully with parenteral administration of streptomycin (2 Gm. daily intramuscularly) and penicillin (100,000 units every three hours).[481]

Shock secondary to peritonitis was experimentally produced in dogs by introducing feces into the peritoneal cavity.[482] In untreated animals shock appeared to be due to diminution of plasma volume, with reduction in cardiac output and fall in arterial pressure. In animals treated with plasma there was a fall in blood pressure in the presence of normal blood volume and cardiac output. In the first instance shock was probably due to loss of fluid into the peritoneal cavity, in the second to loss of resistance in the peripheral vascular bed. In a study of 35 patients with severe peritonitis, 12 of whom eventually died, the plasma volume frequently was reduced.[483] Parallel changes were noted in the total circulating plasma protein and a proportionately greater fall in plasma albumin. The main causes of the volume reduction were ileus and exudation of plasma into the peritoneal cavity. There was evidence that reduction of blood volume produced renal injury and that renal failure sometimes was an important cause of death.

Six patients with so-called benign paroxysmal peritonitis are reported on.[484] The disease begins in early life and recurs in episodes for many years with paroxysms of abdominal pain, signs of peritoneal irritation, fever of 100 to 105 F., leukocytosis and inspiratory chest pain. In 3 patients operation disclosed hyperemia or edema of the peritoneum, with or without serous or serofibrinous exudate. There seems to be a familial

480. Altemeier, W. A.: The Treatment of Acute Peritonitis, J. A. M. A. **139**:347 (Feb. 5) 1949.

481. Schaff, B.; Spendlove, J. G., and Todd, J. W.: Treatment of Peritonitis with Parenteral Streptomycin and Penicillin, Am. J. Surg. **77**:63, 1949.

482. Ebert, R. V.; Hagen, P. S., and Borden, C. W.: The Mechanism of Shock in Peritonitis, Surgery **25**:399, 1949.

483. Theron, P. H., and Wilson, W. C.: Blood Changes in Peritonitis, Lancet **1**:172, 1949.

484. Siegal, S.: Benign Paroxysmal Peritonitis—Second Series, Gastroenterology **12**:234, 1949.

tendency. The disorder is thought by the author to be related to allergy. Two additional patients are described with similar clinical manifestations.[485]

*Vascular Accidents.*—Twenty-three cases of tuberculous aneurysm of the abdominal aorta and 41 reported instances of an abdominal aortic aneurysm rupturing into the gastrointestinal tract are reviewed, and a tuberculous aneurysm of the abdominal aorta which ruptured into the stomach is recorded.[486]

*Large Intestine Colic Due to Sympathetic Deprivation.*—Two cases are described of men, aged 66 and 58, with symptoms strongly suggesting obstruction of the distal portion of the colon by a carcinoma.[487] In each instance operation disclosed a normal colon and extensive and entirely unsuspected malignant disease involving the region of the crura of the diaphragm, the celiac axis and semilunar ganglions. The primary carcinoma in the first patient arose in the pancreas; the origin of the lesion in the second patient was not determined conclusively. It is suggested that the subdiaphragmatic growth had interrupted the sympathetic supply to the large intestine, so that the parasympathetic innervation, which in the distal part of the colon arises in the second and third sacral nerves, was allowed to act unopposed.

*Hernia.*—Emergency operation was required in 40 per cent of 500 cases of incarcerated and strangulated hernia, with a mortality rate of 16.8 per cent.[488] Manual reduction was accomplished in 60 per cent of the series, with a mortality rate of 2.4 per cent.

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485. Heineken, T.: Benign Paroxysmal Peritonitis: Report of 2 Cases, J. M. Soc. New Jersey **44**:451, 1947.

486. Scott, J. W.; Maxwell, E. S., and Grimes, A. E.: Tuberculous False Aneurysm of the Abdominal Aorta with Rupture into the Stomach, Am. Heart J. **37**:820, 1949.

487. Ogilvie, H.: Large Intestine Colic Due to Sympathetic Deprivation, New Clinical Syndrome, Brit. M. J. **2**:671, 1948.

488. Requarth, W., and Theis, F. V.: Incarcerated and Strangulated Inguinal Hernia: Critical Survey of 500 Consecutive Cases with Treatment by Nonsurgical (Taxis) and Surgical Procedures, Arch. Surg. **57**:267 (Aug.) 1948.

# News and Comment

## NOTICES

**American Association for the Advancement of Science.**—The American Association for the Advancement of Science will hold its one hundred and seventeenth meeting in Cleveland, Dec. 26 to 30, 1950. The program will include two sessions on steroid hormones, one on medicinal chemistry, a four session symposium on "Biological Effects of Radiation", and four sessions on a joint program with the Scientific Section of the American Pharmaceutical Association. Information on housing and advance registration may be found in *Science* and *The Scientific Monthly*. Those who wish to attend are urged to register in advance.

**Postgraduate Course in Diseases of the Chest.**—The Council on Postgraduate Medical Education and the New York State Chapter of the American College of Chest Physicians will sponsor the Postgraduate Course in Diseases of the Chest, Nov. 13 to 18, 1950, at the Hotel New Yorker, New York. The course will include lectures on modern diagnostic procedures in chest diseases, surgery in tuberculosis, nontuberculous infections, pulmonary and mediastinal tumors, bronchopulmonary suppurations, pulmonary emphysema and asthma, the heart in relation to pulmonary diseases, and industrial pulmonary diseases. Further information may be secured from the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10.

**The Association of Military Surgeons of the United States.**—The 1950 convention of The Association of Military Surgeons of the United States will be held Nov. 9 to 11, 1950, at the Hotel Statler, New York. Civil defense, the defense role of the physician, aviation medicine, rehabilitation, military medicine, surgery, sanitation and emergency use of newest therapeutic and prophylactic agents will be discussed. Problems of the Medical Reserve will also be considered in several sessions.

## GENERAL NEWS

**Federal Grants for Research.**—Presidential approval of the omnibus appropriations bill for 1951 makes available $3,600,000 for research with the new drugs, cortisone and ACTH. This sum is allocated for research grants to nonfederal institutions and scientists. Grants will be made largely for study of the compounds as related to arthritis and cancer and mental and neurological, metabolic and cardiovascular diseases, as well as for basic laboratory investigations on the general biologic effects of the compounds. These grants will be administered through the United States Public Health Service's Research Grants and Fellowships Division of the National Institutes of Health. Applications will be evaluated by specialized study sections in each of the research fields, and the appropriate National Advisory Council will make the final recommendation. Deadline for receipt of applications is Nov. 1, 1950.

# Book Reviews

**Differentialdiagnose der inneren Medizin.** By Prof. Dr. Med. Otto Naegeli. Price, $9. Pp. 794, with 189 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

In 1942, after Naegeli's death, the second edition of his book was prepared by his pupils according to his wishes. In an initial chapter, general aspects of differential diagnosis are discussed by Rohr. He also deals with the differential diagnosis of the diseases of the blood as well as of diseases of the lymph nodes and tumors of the mediastinum, of diseases of the throat and related conditions and of diseases of the spleen. Gloor-Meyer discusses the differential diagnosis of diseases of the liver and bile passages and of abdominal diseases. Gsell presents the diseases of the lungs and the esophagus and infectious diseases of the joints. Holzmann contributes the differential diagnosis of diseases of the heart and blood vessels and Gloor that of diseases of the kidneys and urinary passages. The differential diagnosis of diseases of the nervous system and of diseases of the organs of inner secretion is elaborated by F. Lüthy.

It is pointed out that in the whole field of the natural sciences it is becoming more widely recognized that a concept which represents everything as simple is unjustified. If the reviewer understands the somewhat awkward sentence correctly, it means that the old slogan, "Simplicity is the sign of truth," can have only limited application.

The most important feature of the book is the outline of diseases into groups. These groups are (1) inflammations, (2) intoxications, (3) malignant tumors, (4) systematic hyperplasias of the lymphatic or myelotic apparatus, (5) disturbances of hormonal relations, (6) allergic-anaphylactic disorders, (7) avitaminoses and deficiency diseases and (8) diseases of isolated organs but with widespread consequences. While it is recognized that the sketching of these groups is rather incomplete, it is regarded as most important that the physician first of all should try to place the patient's ailment into one or more of these groups or to exclude several of the groups. Then various approaches to the differential diagnosis are given.

A more detailed presentation of the different approaches to the differential diagnosis under the various main headings is hardly possible. As is to be expected, the book furnishes much valuable information. A few remarks may be cited which will show the character of the work. The statement is made that an enlargement of lymph glands is often neglected. The diagnosis of status lymphaticus or of status thymicolymphaticus is regarded as very difficult and almost always uncertain. While biopsy of a lymph node may be decisive, it is pointed out that even first class authorities may differ widely in their interpretation. Speaking of diseases of the spleen, the lack of attention to percussion of the spleen is deplored. Banti's disease is not recognized as an entity. The situation is this: The clinician assumes a specific histologic picture while the pathologist regards a specific clinical course as characteristic, with the result that each one shifts the burden of proof to the other. A transition of icterus simplex, assumed to be due to a lesion limited to the cells of the liver, to cirrhosis is not regarded as proved.

As is to be expected, a number of errors may be pointed out, but most of them are of little importance. Sometimes an important feature is omitted in a place where

the reader would be expected to find it and the disease is mentioned elsewhere. For instance, in relation to the factors leading to evacuation of blood with the stool, Meckel's diverticulum, intussusception or polyps are not mentioned. It should be noted that intoxication with atropine can cause fever; also, the value of the cutaneous test in undulant fever seems to be overrated. The differential diagnosis of those congenital lesions of the heart which may be benefited by surgical procedures needs further elaboration, and some consideration could have been given to the lesions of the abdominal wall. Coccidiosis, histoplasmosis and toroplasmosis have not been considered. The chapter on "peritoneism" seems to deserve special mention. On the whole the book should prove a welcome addition to a physician's library.

**Der Morbus Besnier-Boeck-Schaumann.** By Stefan J. Leitner. Price 38 Swiss francs. Pp. 264, with 90 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 6, 1949.

In the introduction the author calls attention to the fact that various localizations of the disease have been known for a long time. But the cooperation of dermatologists, ophthalmologists, internists, surgeons and pathologists of recent times was necessary to provide an understanding of the details of this well characterized general disease. Schaumann is credited with the recognition of this fact. The nomenclature is discussed, and a preference is stated for the designation of "chronic epithelioid cellular granulomatosis." A systematic localization of the lesions is given. The lesions may be situated in (1) the eye, (2) the skin, (3) the bones, (4) the lymph nodes, (5) the lungs and (6) other organs. The detailed features of the disease are described on the basis of 36 cases.

It is stated that pathologists stress the preference of localization in organs rich in reticuloendothelial cells. The gross and the histologic lesions are described and illustrated by instructive sections. In 72 postmortem examinations such epithelioid cellular granulomas were found. In some of these the involvement of heart or brain was regarded as a cause of death. It is of interest that of the 67 cases in which the age of the patient is given 7 patients were less than 20 years of age; the youngest was 15 years of age. In the book it is regarded as established that uveoparotitis (Heerfordt syndrome) is a manifestation of epithelioid cellular granuloma and probably the Mikulicz syndrome, whereas the Sjögren syndrome is not, although it can have some features in common with uveoparotitis and the Mikulicz syndrome. It is pointed out that a participation of cranial and spinal nerves is not limited to the Heerfordt syndrome. The central nervous system also may be affected, with a differentiation into tumor-like or perivascular lesions. Various types of skin manifestations are described as well as the involvement of mucous membranes. The localization in lymph nodes may be limited to those of the hilus of the lungs. The manifestations of epithelioid cellular granulomatosis in the lungs, seen in the majority of cases, are described more fully. A chapter is devoted to ostitis multiplex cystoides (Jüngling's disease) found in many cases. Under the heading "involvement of the blood forming-organs" changes in bone marrow, liver and spleen are described. The numerical relation of the bone marrow cells is registered in a table, and the blood picture is discussed in a later chapter, also with tabulation limited on the whole to monocytes and eosinophils. The localization in kidneys, gastrointestinal tract, pancreas and heart is described, the last being considered most fully. The results of spirometric examinations are tabulated. Other endocrine glands, besides the pancreas, may be the seat of the characteristic lesions. Such lesions were found in the thyroid and parathyroid glands, in the

testes and the epididymis, in the adrenal glands and in the hypophysis. They also have been reported in the uterus and mammary glands as well, if rarely in striated and smooth muscles. Changes in blood proteins and blood calcium are discussed.

With reference to the main etiologic factors, it is stated that the histologic structure of the lesion speaks rather in favor of a tuberculous nature. In this connection a consideration of paraffinoma might not have been amiss. The pros and cons of the tuberculous nature of the epithelioid cellular granuloma are discussed extensively. But even if the lesions may be referable to a variant of tubercle bacilli or to some of their chemical constituents, the disease, nevertheless, constitutes an entity different from the usual forms of tuberculosis. It is concluded that for any other etiologic conception than that of an atypical tuberculosis no arguments could be advanced which were anywhere near as good as those speaking for an atypical tuberculosis.

The prognosis, while usually favorable as to restitution to normal, sooner or later may be bad. Death may be due to involvement of brain or heart or to extensive lesions of the lungs with consequent breakdown of the right side of the heart. A transition to usual tuberculosis also may lead to death. Aside from such a fatal outcome the ocular lesions, on healing, may leave severe visual defects. The author is in favor of placing patients with this disease into a sanatorium. The book is well worth reading.

**Gastroscopy: The Endoscopic Study of Gastric Pathology.** By Rudolf Schindler, M.D., F.A.C.P. Price, $20. Pp. 433, with 366 illustrations. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1950.

This is the second edition of the standard American text on gastroscopy, the first having appeared in 1937. The general scheme of presentation has not been altered, but many important additions and revisions are included.

The description of the optics of the gastroscope, the technic of gastroscopic examination and orientation in regard to the stomach are all written with enviable clarity. Indications for gastroscopy are very adequately discussed, and the relative value of gastroscopy and roentgen examination in the diagnosis of the various diseases of the stomach is constantly and fairly stressed. An important addition in this edition of the book is the correlation by Dr. Schindler of the gastroscopic and the histologic picture in chronic gastritis; this group of facts is the clinching evidence for the existence of the disease entity chronic gastritis. Another important contribution is the evidence accumulated to show that many patients with so-called nervous stomach are suffering from chronic gastritis. The chapter on carcinoma is generously supplied with gastroscopic illustrations, case histories and pathologic specimens and, indeed, contains a wealth of material on the subject generally.

This beautiful, exacting presentation should be included in the library of every internist, even though he is not interested in doing gastroscopy or learning the technical aspects of the subject.

**The Practice of Urology.** Two Volumes. By Harry C. Rolnick, M.D. Price, $24. Pp. 1,245, with 1,350 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C.2.; 2083 Guy St., Montreal, Canada, 1949.

This new textbook of urology covers well the progress in the field which has been attained in the past decade. The section on transurethral surgery of the

bladder neck is especially thorough and reflects the views of not only the enthusiastic resectionist but also the general urologist. The newer concept of malignancy, especially of the prostate gland, is thoroughly and adequately discussed. Modern surgical procedures in urology are dealt with throughout the book.

The chemotherapy and antibiotic therapy used in the modern treatment of urinary infections are gone into in detail and brought up to date. Preoperative and postoperative care and examination are dwelt on in detail, and all the newer methods of fluid control, protein balance and other methods are compactly assembled. Also the section on laboratory procedures in diagnostic urology is very good.

In the opinion of this reviewer "The Practice of Urology" is a complete coverage of the field, both medical and surgical. It is well indexed, and it appears to be an excellent textbook and a fine reference.

**Principles and Practice of Therapeutic Exercises.** By Hans Kraus, M.D. Price, $6.50. Pp. 309, with 94 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

The field of therapeutic exercise has been of increasing interest to members of the medical profession in the last few years. A great need has arisen for adequate and detailed information on exercise therapy. The author states that the objective of this book is to suggest to newcomers to the field a basis for rational prescription and application of exercises.

This book attempts to describe some basic qualities of muscular function, outlines methods of testing and measuring these fundamental qualities, and illustrates various technics of exercise, aiming at improvement of function of muscles and joints. There are numerous line drawings illustrating the exercises, and an effort is made to indicate the qualities of muscle function as well as the movement performed. A large part of the book is devoted to the practical application of therapeutic exercises to a wide range of specific pathologic conditions. Some of the conditions which the author discusses and which might be of interest to the internist are pain of various types in the back, torticollis, subdeltoid bursitis, acute muscular strains, hemiplegia and multiple sclerosis. The author gives the reader the benefits of his broad clinical experience in this field.

Although the greater portion of the book is devoted to exercises for local lesions, the author does discuss briefly the value of general exercises to keep patients in good physical condition. He deplores the neglect to use general convalescent exercises and suggests that preoperative preparation of the patient, with proper exercises, can be of considerable value.

Certainly all physicians should be more familiar with therapeutic exercise from the medical viewpoint, and this book is the most extensive one yet prepared on the subject. It is worthy of careful perusal.

**Quinidine in Disorders of the Heart.** By Harry Gold, M.D. Price, $2. Pp. 115. Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 49 E. 33d St., New York 16, 1950.

In this small book the author has accomplished in a most satisfactory fashion his stated intention of providing a guide for the use of quinidine in the treatment of disorders of the heart. He has presented clearly the issue of maintained therapy versus treatment of the individual attack in the paroxysmal arrhythmias. The complexities which arise in any attempt to analyze the consequences of combined

digitalis and quinidine therapy are defined but not resolved. However, an attractively rational position is assumed on this disputed subject. The author proposes to avoid the simultaneous use of quinidine and digitalis whenever possible, especially when large doses of both may be necessary.

Perhaps the most significant flaw in the presentation is its air of therapeutic optimism. This may be the product of prolonged enthusiastic and intelligent use of quinidine, but it seems likely that, even after reading this book, the most apt pupil will find in his own experience abundant frustrations and failures. Had the author been obsessed with these things, however, this excellent monograph would not have been written.

**Water and Salt Depletion.** By H. L. Marriott, M.D. Price, $2. Pp. 80, with 11 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

Dr. Marriott does physicians a real service in this fine monograph by presenting the complicated subject of water and salt depletion in a lucid and readily understandable fashion. The most valuable part of the work is the correlation of clinical signs and symptoms with the type and degree of fluid imbalance in such a way as to be useful in diagnosis and treatment. A clear differentiation is made between water depletion and salt depletion, which is also helpful in planning treatment intelligently. Basic physiologic concepts and clinical observations are made easily understandable by the liberal use of well planned charts and diagrams. The author is perhaps a little overenthusiastic about the use of the urinary chloride determination.

This monograph should be welcomed particularly by all who have become discouraged and confused in trying to obtain a practical knowledge of water and electrolyte balance.

**Medical Clinics of North America: Symposium on Pediatrics; Chicago Number.** By various authors. Pp. 306, with 54 illustrations. W. B. Saunders Company, W. Washington Sq., Philadelphia 5, 1950.

This volume follows the usual style of the "Medical Clinics of North America" and contains a series of miscellaneous articles dealing with pediatric subjects. The articles seem up-to-date and deal with such important subjects as parenteral fluid therapy, recent advances in the treatment of leukemia and many others of equal interest.

**A Manual of Cardiology.** Second edition. By Thomas J. Dry. Price, $5. Pp. 355, with 97 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1950.

If the author of this pocket-sized manual were not eminently well informed on his subject, so much that is important could not be said in so few words. Despite its small size, this volume is not simply an outline of cardiology. The discussions of various phases of heart disease are adequate, up to date and well documented.

While there is a chapter on "The Normal Electrocardiogram and the Mode of Production of Abnormal Patterns," electrocardiographic illustrations are scattered throughout the book, demonstrating the various patterns of the conditions under discussion. The section on congenital heart disease contains beautiful diagrams, roentgenograms and other pertinent data to make this difficult subject more understandable.

The chapter on rheumatic heart disease includes a discussion of all the "collagen diseases" and has been revised so recently that treatment with cortisone is discussed. Also the results of the radically changed management of subacute bacterial endocarditis have been brought up to date.

This new book of Dr. Dry can be heartily recommended to those looking for a condensed but authoritative manual to help them in the diagnosis and management of heart disease.

**A Primer for Diabetic Patients.** Revised ninth edition. By Russell M. Wilder, M.D. Price, $2.25. Pp. 200. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1950.

Wilder's book, already a classic in its field, having first appeared in 1921, now comes out in the ninth edition. The same general format is followed and the contents are much as in previous editions, but, as Dr. Wilder states in the preface, he is now inclined to be more liberal in dietary recommendations and to advise somewhat less rigidity than formerly in the control of glycosuria. These changes, of course, apply only to those patients who are taking insulin. This little volume remains, as before, very useful for both physician and patient.

**Textbook of Medical Treatment.** By various authors. Price, $8.50. Pp. 999, with 40 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1949.

This volume contains sections written by rather a large number of British authorities and presumably represents the best British practice. The authors all write well, as the English do, and the book is extremely readable. One is struck, however, by the fact that whereas the imprint bears the date 1949, many of the advances, especially in drugs and antibiotics, which have been recognized for a year or more in America are not mentioned. Streptomycin, for example, is said to be not yet available for private use. The crystalline procaine penicillins so generally satisfactory here are apparently unknown in Britain, where they seem still to be struggling with the old oil and wax mixtures. In cardiac therapy the use of tincture of digitalis is advocated as the most useful preparation, whereas it obviously is a nuisance compared to tablets of the leaf or to digitoxin. Under Hodgkin's disease the nitrogen mustards are not discussed, whereas a paragraph is devoted to Gordon's vaccine. Under cirrhosis of the liver the Talma-Morison operation, a long-forgotten failure in the experience of most physicians, also rates a fourth of a page. And so on through the book.

Perhaps all this merely represents conservatism on the part of the contributors. At any rate a very good feature is the emphasis on the elementary concepts of therapy: nursing, rest, hygiene, diet, etc.

**Treatment in Proctology.** By Robert Turell. Price, $7. Pp. 248, with 85 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1949.

This profusely and beautifully illustrated book seems to be just what the general physician as well as the proctologist can use to great advantage. It is not primarily a book on surgery, and there are no long detailed discussions of surgical technic. However, diagnosis, indications and preoperative and postoperative treatment are fully discussed. Of particular value are the comprehensive discussions of pruritus, hemorrhoids, polyps, stricture and other common conditions which so often require attention. Comprehensive bibliographies after each chapter are a feature.

**Annals of the New York Academy of Sciences: Antibiotics Derived from Bacillus Polymyxa.** Volume 51, article 5. By Long and others. Pp. 853-1,000. New York Academy of Sciences, American Museum of Natural History, Central Park W. and 77th St., New York 24, 1949.

This issue of the *Annals of the New York Academy of Sciences* contains eighteen excellent papers which cover in detail the present status of the polymyxins. The following subjects are included: (1) antibacterial activity in vitro and in vivo; (2) isolation and production; (3) relation between polymyxin and aerosporin; (4) chemical nature; (5) assay; (6) pharmacology, and (7) clinical effectiveness in a variety of infections.

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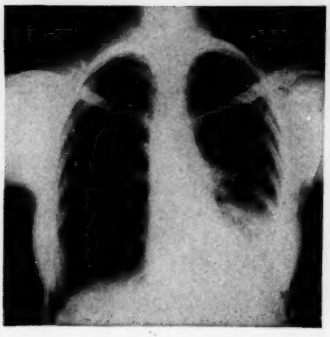

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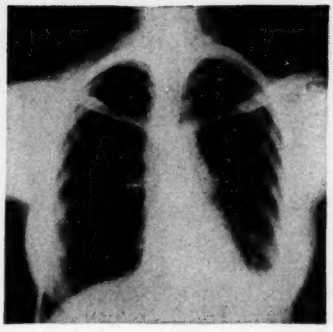

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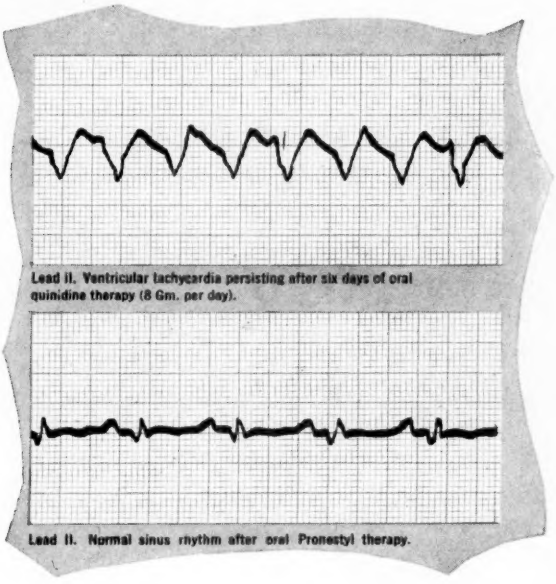

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